A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF PITAVASTATIN AND ATORVASTATIN IN DYSLIPIDEMIC PATIENTS

DISSERTATION

Dissertation submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai

In partial fulfillment of the requirements

For the award of the degree of

MASTER OF PHARMACY

IN

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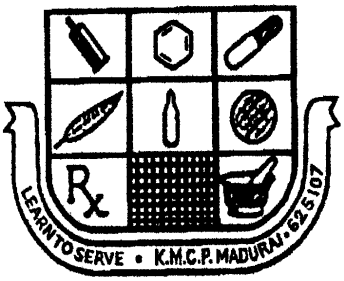

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

K.M. COLLEGE OF PHARMACY

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CERTIFICATE

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF PITAVASTATIN AND ATORVASTATIN IN DYSLIPIDEMIC PATIENTS,** submitted by **Mr.S.SHAIKSIKKENDER ABDULLAH,** in partial fulfilment for the degree of **"Master of Pharmacy in PHARMACY PRACTICE"** under The Tamilnadu Dr. M.G.R Medical University, Chennai, at **K.M. College of Pharmacy**, Madurai, is a bonafide work carried out by him under my guidance and direct supervision during the academic year of **April 2014 – 2015**. This dissertation partially or fully has not been submitted for any other degree or diploma of this university.

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"I humbly submit this work to the Almighty"

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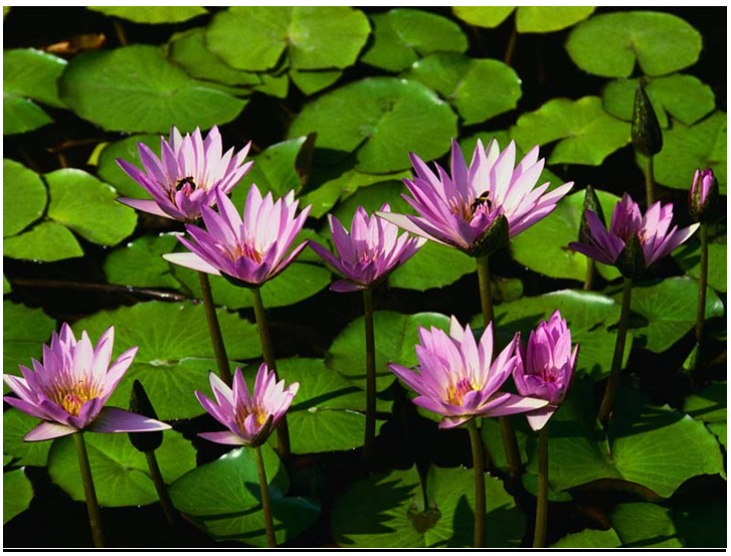


THE ALMIGHTY AND MY FAMILY

CHAPTER I

INTRODUCTION

1. INTRODUCTION

Lipids are fats that are either absorbed from food or synthesized by the liver. Triglycerides (TGs) and cholesterol contribute most to disease, although all lipids are physiologically important[1].

Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-associated conditions, such as coronary heart disease (CHD), Ischemic cerebrovascular disease, and peripheral vascular disease. Although the incidence of these atherosclerosis-related events has declined in the United States, these conditions still account for the majority of morbidity and mortality among middle-aged and older adults. The incidence and absolute number of annual events will likely increase over the next decade because of the epidemic of obesity and the aging of the U.S population. Dyslipidemia, including Hyperlipidemia (hypercholesterolemia) and low levels of high-density-lipoprotein cholesterol (HDL-C), are major causes of increased atherogenic risk: both genetic disorders and lifestyle (sedentary behaviour and diets high in calories, saturated fat and cholesterol) contribute to the dyslipidemia seen in developed countries around the world.

Recognition that dyslipidemia is a risk factor has led to the development of drugs that reduce cholesterol levels. There drugs provide benefit in patients across the entire spectrum of cholesterol levels, primarily by reducing levels of low-density lipoprotein cholesterol (LDL-C). In well-controlled clinical trials, fatal and non-fatal CHD events and strokes were reduced by as much as 30% and 40%[2-6].

Clinical trial data support extending lipid-lowering therapy to high-risk patients whose major lipid risk factor is a reduced plasma level of HDL-C, even if their LDL-C level does not meet the existing threshold values for initiating hypolipidemic drug therapy[7]. In Patients with low HDL-C and average LDL-C levels, appropriate drug therapy reduced CHD endpoint events by 20% to 35%[4,8,9]. Since two-third of patients with CHD in the United States have low HDL-C levels (<40 mg/dl), it is important to include low-HDL patients in management guidelines for dyslipidemia, even if their LDL-C levels are in the normal range[10].

CHAPTER II

SUBJECTIVE INTRODUCTION

2. SUBJECTIVE INTRODUCTION

Hyperlipidemia is an increase (hyper) in the lipids (lipi), which are a group of fats or fat like substances in the blood (demia). Cholesterol and the triglycerides are the two lipids in the blood. Elevation of one or both of these lipids is seen in hyperlipidaemia. Serum cholesterol levels above 240 mg/dL and triglyceride levels above 150 mg/dL are associated with atherosclerosis[11].

Hyperlipidemia is defined in terms of class or classes of elevated lipoproteins in the blood, the term Hyperlipoproteinemia is used Hypercholesterolemia refers to high triglyceride level in the blood. These statistics illustrate the importance of identifying and managing risk factors for CHD. The major conventional risk factors are elevated LDL-C,reduced HDL-C, cigarette smoking, hypertension, type 2 diabetes mellitus, advancing age, and a family history of premature(men<55 years; Women <65 years) CHD events in a first-degree relative. Control of the modifiable risk factors is especially important in preventing premature CHD.

Observational studies suggest that modifiable risk factors account for 85% of excess risk (risk over and above that of individuals with optimal risk-factor profiles) for premature CHD[12]. The presence of one or more conventional risk factors in 90% of patients with CHD belies claims that a large percentage of CHD, perhaps as much as 50%, is not attributable to conventional risk factors.

Severe hypertriglyceridemia (i.e., triglyceride levels of >1000 mg/dl) required therapy to prevent pancreatitis. Moderately elevated triglyceride levels (150 to 400 mg/dl) also are of concern because they often occur as part of the metabolic syndrome, which includes insulin resistance, obesity, hypertension, low HDL-C levels and substantially increased CHD risk. The atherogenic dyslipidemia in patients with the metabolic syndrome is characterized by moderately elevated triglycerides, low HDL-C levels, and lipid-depleted LDL (sometimes referred to as “small, dense LDL”) [13,14]. The metabolic syndrome affects-25% of adults and is common in CHD patients: hence, identification of moderate hypertriglyceridemia in a patient, even if the total cholesterol level is normal, should trigger an evaluation to identify this disorder[15,16].

CLASSIFICATION OF HYPERLIPIDEMIA

Hyperlipidemia is classified according to the Frederickson classification which based on the pattern of lipoproteins on electrophoresis or ultracentrifugation. It was later adopted by the World Health Organization. (WHO)

Primary Hyperlipidemia

Upto 60% of the variability in the serum fasting lipids may be genetically determined although expression is often influenced by interaction with environmental factor. The familial disorders can be classified as follows.

Hyperlipoproteinemia Type I

This is the very rare (also known as Buerger greets syndrome, primary Hyperlipoproteinemia of familial hypercholesterolemia) is due to a deficiency of lipoprotein lipase (LPL) or altered lipoprotein C2 resulting in elevated chylomicrons, the particles that the transfer fatty acids from the digestive tract to the liver. LPL is also responsible for the initial breakdown of endogenously made triglycerides in the form of VLDL. Defect in LPL also result in elevated VLDL. Its prevalence is 0.1% of the Population.

TABLE.I

World Health Organization classification of Hyperlipoproteinemia[17]

Type	Plasma Cholesterol	LDL Cholesterol	Plasma triglycerides	Lipoprotein abnormality
I.	Raised	Low or normal	Raised	Excess chylomicrons
II a	Raised or normal	Raised	Normal	Excess LDL
II b	Raised	Raised	Raised	Excess LDL & VLDL
III	Raised	Low or normal	Raised	Excess chylomicrons &remnants& IDL
IV	Raised	Normal	Raised	Excess chylomicrons & VLDL
V	Raised	Normal	Raised	Excess chylomicrons & VLDL

Hyperlipoproteinemia type II

Hyperlipoproteinemia type II, by for the most common form, is further classified into type II a and type II b, depending mainly on whether there is elevation in the triglyceride level in addition to LDL cholesterol.

Type II a

This may be sporadic (due to dietary factors) polygenic, or truly familial as a result of mutation, either in the LDL receptor gene on chromosome 19 (0.2% of the population) or the ApoB gene (0.2%). The familial form is characterized by Tendon Xanthoma, Xanthelesma and premature Cardio Vascular diseases.

Type II b

The high VLDL levels are due to over production of substrates, including triglycerides acetyl Co-A and on increase in B – 100 syntheses. They may also be caused by the decreased clearance of LDL. Its prevalence in the population is 10%.

Hyperlipoproteinemia type III

This form is due to high triglycerides. It is also known as hypertriglyceridemia. According to the NCEP-ATP III detention of high triglycerides (>200 mg/dl). Its prevalence is adult 16% of adult population.

Hyperlipoproteinemia type IV

This type is very similar to type 1, but with high VLDL in addition to chylomicrons. It is also associated with glucose intolerance and Hyperurecemia.

Unclassified forms

Non classified forms are extremely rare

- Hypo α– lipoproteinemia
- Hypo β– lipoproteinemia

Secondary Hyperlipidemia

In the class of secondary hyperlipidaemias there have a number of disorders, dietary indiscretion or as a side effect of drug therapy. These account for up to 40% of hyperlipidaemias.

Disease states:

Many of the disease states associated with secondary hyperlipidaemias are

- Non – insulin dependent diabetes
- Insulin dependent diabetes
- Hypothyroidism
- Pregnancy
- Alcohol abuse
- Chronic renal failure
- Cardiac transplantation
- Myeloma

Drugs:

A large number of drugs can affect serum lipid and lipoprotein concentration, some of them are

- Amiodarone
- Androgens
- B-Adreno receptor blockers
- Cyclosporine
- Diuretics
- Thiazides
- Loop diuretics
- Glucocorticoids
- Oral Contraceptives
- Vitamin A derivate

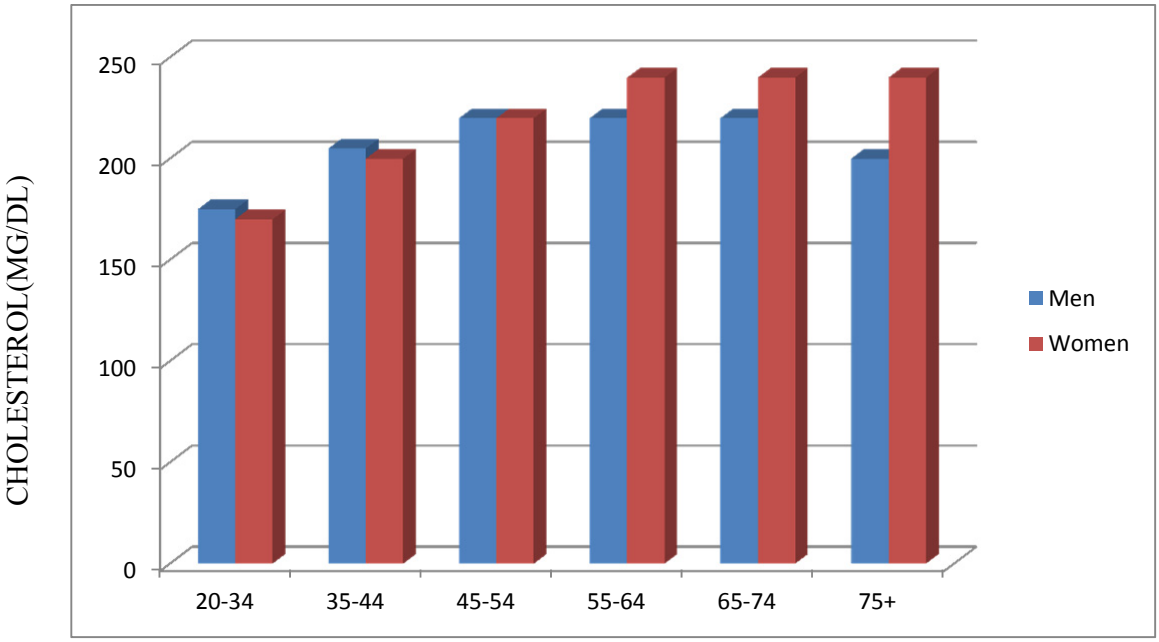
EPIDEMIOLOY[33]

Total cholesterol and LDL cholesterol increase throughout life in men and women representing an atherogenic pattern characteristic of Western society diets (Fig.1)[19] Based on the National Health and Nutrition Examination Survey (NHANES1999-2000) and the ATP III guidelines, slightly more than 50% or nearly 105 million American adults over 20 years of age have total cholesterol levels of 200 mg/dl or higher. [19,20,21] only about one-third are aware that they have hypercholesterolemia, and 12% were on therapy for hypercholesterolemia. Changes in the NCEP guidelines have increased the number of persons eligible for therapeutic lifestyle changes (TLCs) or lipid-lowering therapy by millions.

NCEP estimates that only 26% of patients have an optimal LDL cholesterol (<100 mg/dl) and that large numbers of patients are either untreated or undertreated. Unfortunately, the patients at highest risk are less likely to the treated to desirable levels of LDL[22]. Although these numbers appear staggering in their enormity, substantial progress has been made, and the number of Americans with a desirable blood cholesterol level (<200 g/dL) hasraised to 49% from 45% in the earlier survey (1976-1980), whereas the average total cholesterol level in this country has fallen from 220 mg/dL in 1960 to 203 mg/dL in 1988-1994. Unfortunately, there has been little change in total cholesterol between 1994 and 2000. Patients who are at risk but who have not yet experienced their first cardiovascular event (e.g., myocardial infraction [MI]) are termed primary prevention, whereas those manifest vascular diseases are termed secondary intervention.

Data from the Framingham Study and from other studies and from other studies demonstrate that the risk for developing cardiovascular disease is related to the degree of total cholesterol and LDL elevation in a graded, continuous fashion[23]. Hypercholesterolemia is additive to the other non-lipid risk factors for CHD, including cigarette smoking, hypertension, diabetes, low HDL levels, and electrocardiographic (ECG) abnormalities. The presence of established CHD prior MI increases the risk of MI five to seven times that seen in men or women without CHD, and LDL is a significant predictor of subsequent morbidity and mortality[24].

FIG.1



About 50% of all MIs and at least 70% of CHD deaths occur in patients with known CHD, and these patients therefore should be a target for screening, identification, and treatment. Unfortunately, the identification of patients at high risk because of hypercholesterolemia or other lipid disorders is too frequently overlooked because blood lipid levels are not always evaluated in this population even after an event such as MI[25].

A comparison of the United States with other countries shows similar relationships between total cholesterol and LDL and an inverse relationship with HDL and coronary artery disease (CAD) mortality[26]. On a positive note, the U.S.mortality rate is midway among the countries studied, and this country has had the greatest decline in CAD mortality (35% and 40%) in men and women over the last 10 years compared with other countries. A decline in the prevalence of hypercholesterolemia in certain segments of the U.S. population parallels these trends in mortality. LDL and the ration of LDL to HDL also have been used to assess risk, but their use adds little information to total cholesterol alone unless HDL is abnormally high or low. HDL transports cholesterol from lipid-laden foam cells top the liver.

HDL has been shown to be protective for the occurrence of CHD, and an inverse relationship exists between CHD and HDL levels[27]. LDL is enriched with cholesterol esters and is smaller, denser, and more atherogenic than less-dense VLDL. Routine measurement of triglycerides cannot distinguish between the types of VLDL present in plasma. Elevation of triglyceride-rich lipoproteins is associated with low HDL, and this ration predicts increased risk. The 8-year follow-up of the Copenhagen male study found a clear gradient of risk of ischemic heart disease (IHD) with increasing triglyceride levels within each level of HDL cholesterol. When compared with the lowest tertile of triglyceride concentrations, the highest tertile had 2.2 relative risks for IH|D, and the relationship extended across all concentrations of HDL[28].

The Helsinki Heart Study shows the hypertriglyceridemia and low HDL levels are associated with obesity (body mass index [BMI] >26 kg/m2}, smoking, sedentary lifestyle, blood pressure of 140/90mm Hg or greater, and a blood glucose concentration above 4.4 mmol/L and that the benefit of gemfibrozil (risk reduction 68%, p< .03) was confined largely to overweight subjects[29]. Hypertriglyceridemia in certain instances e.g., diabetes mellitus, nephrotic syndrome, and chronic renal disease and perhaps in women is associated with increased cardiovascular risk. This is thought to be a consequence of the presence of lipoproteins and of hypertriglyceridemia being a marker for them, since triglycerides usually are not independently predictive for CHD[30].

LIPIDS AND LIPOPROTEINS

Lipid Terminology

Some of the complexity for the beginner striving to understand lipid metabolism may be due to the terminology used in relation to this topic. For example, the terms “cholesterol” and “lipid” may be considered by some to be synonymous, and as such, are used without distinction in reference to dyslipidemic conditions. Cholesterol is one of the major lipid particles in the body; the other is triglyceride (TG). Both of these particles serve important functions; however as insoluble molecules, they must be transported in the blood in complexes known as lipoproteins[32]. Plasma lipoproteins are composed of a core of TG and cholesterol ester, enveloped by a surface coat of phospholipid, unesterified

("free") cholesterol, and special proteins called Apo lipoproteins (or Apo proteins). The term "lipoprotein" refers to this unique combination of "lipid" and "protein". Several lipoprotein complexes exist, and each is identified according to its density, lipid composition, and the Apo lipoproteins on the surface of the particle.

The five mainclassifications of lipoproteins are chylomicrons, very low-density lipoprotein cholesterol (VLDL), intermediate-density lipoprotein cholesterol (IDL), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). In the laboratory, total cholesterol, TG, and HDL are measured directly, from which a calculated estimation of VLDL and LDL cholesterol are derived. These measurements of VLDL and LDL are based on a fasting TG level and are valid only when the TG level is less than 400 mg/dL (5 mmol/L). This explains the requirement for a fasting blood sample (overnight fast of 12 hours) to determine blood lipid levels. Direct measurement of VLDL and LDL is also possible; however, due to their high cost and technical complexity, these are performedprimarily in reference laboratories.

CLASSIFICATION OF LIPOPROTEINS

Although cholesterol and TG serve several important functions within the body, they are insoluble particles and must be packaged into lipoproteins in order to circulate in the plasma, from sites of synthesis or absorption to sites of use. The core of the lipoprotein, containing cholesterol ester and TG, is nonpolar and hydrophobic, and the outer layer of the lipoprotein particle (contain free cholesterol, phospholipid, and specific Apo lipoproteins), is polarized, permitting the lipoprotein particles to be transported in the circulation. Apolipoproteins (apo) such as apoB, apoC and apoE, coat lipoprotein particulars and serve a number of functions including the transport of lipids in the blood and recognition of lipoprotein particles by enzymes which process or remove lipids from the lipoprotein particles. For example, apoC-II activates the enzyme lipoprotein lipase (LPL), which removes TG from lipoprotein particles such as chylomicrons and VLDL.

Each lipoprotein class (chylomicrons, VLDL, IDL, LDL, and HDL) varies in sizes, density and lipid composition within the core of the particle. Within the main classes of lipoproteins, there may be further differentiation in to subclasses, but for the purposes of this discussion they are referred to as a single lipoprotein.

Chylomicrons and VLDL are the largest, most floating particles, having more TG within their core; in contrast, LDL and HDL have more cholesterol ester within their core and hence, greater particle density. Table II shows the lipoprotein classification, including the major lipid component, apolipoprotein associated with each particle, and the source of the particle.

TABLE II

CHARACTERSTICS OF THE MAJOR LIPOPROTEIN CLASSES

Lipoprotein	Density(g/dl)	Diameter(nm)	Lipid%		
			Tg	Chol	PL
Chylomicron	0.95	75-1200	80-95	2-7	3-9
VLDL	0.95-1.006	30-80	55-80	5-15	10-20
IDL	1.006-1.019	25-35	20-50	20-40	15-25
LDL	1.019-1.063	18-25	40-50	40-50	20-25
HDL	1.063-1.210	5-12	15-25	15-20	20-30

Chylomicrons

Chylomicrons are produced in the intestinal lumen following the absorption of digested fat. They are the largest lipoprotein and are rich in TG. Because of their particle size, chylomicrons scatter more light and may cause the serum to take a cloudy appearance after meals or in patients with dyslipidemic syndromes characterized by the inability to catabolize chylomicrons and TG rich lipoproteins. Chylomicrons are transported in the blood to tissues such as skeletal muscle, fat, and the liver. The capillary beds of these tissues contain high concentrations of LPL. LPL hydrolyzes TG in the chylomicrons into free-fatty acids that are either oxidized by the muscle cells to generate energy, stored in adipose tissue, oxidized in the liver, or used in hepatic VLDL synthesis[33]. Once the chylomicrons have been processed by LPL, the TG-depleted chylomicron is called a remnant particle, which is then transported to the liver for further processing.

VLDL and IDL Cholesterol

VLDL is a lipoprotein particle similar to chylomicrons, which contains a high concentration of TG. VLDL is synthesized from free-fatty acids formed in the

catabolism of chylomicrons in the liver, or from endogenous production of TG[34]. The TG component of VLDL also undergoes hydrolysis by capillary LPL to provide fatty acids to adipose and muscle tissue. The remaining lipid portion is called IDL. IDL is then converted to LDL by enzymatic action of hepatic lipase or is taken up by the liver via the LDL receptor.

LDL Cholesterol

LDL particles carry the majority of the cholesterol in the blood, supplying cholesterol to the cells. LDL receptors in peripheral cells or liver bind with LDL and clear it from the blood. Peripheral cells utilize LDL cholesterol for cell membrane structure and also the production of hormones. LDL is an atherogenic lipoprotein particle, and it is established that higher levels of LDL are associated with increased cardiovascular disease risk[35]. In addition, the heterogeneity of LDL particles composition, due to differences in the amount of cholesterol per particle, suggests that particle size is an important consideration in the atherogenic potential of the LDL. Although the exact mechanism is not fully appreciated, small, dense LDL is thought to be more susceptible to oxidative modification and may therefore be more toxic to the vascular endothelium. A sequence of immunologic and inflammatory events in the arterial wall contributes to atherogenic and the development of atherosclerotic lesions. These advanced lesions occlude coronary artery blood flow and contribute to clinical presentations such as unstable angina or myocardial infarction[36].

HDL Cholesterol

It is well established that increased HDL levels are associated with decreased risk for coronary heart disease, whereas reduced HDL levels increase risk. The cardio protective role of HDL is to facilitate the transfer of cholesterol from atherogenic lipoproteins and peripheral tissues to the liver. Although suggestive of a simple "reverse transport" process, the exact mechanism, dependent on the interactions between HDL apolipoprotein and enzymes activity, is highly complex and poorly understood. HDL particles are synthesized and catabolized in the liver and intestines. Hopeful HDL obtains free cholesterol from peripheral tissues. A circulating enzyme called lecithin: cholesterol acyltransferase promotes the uptake of free cholesterol by HDL by a reaction called esterification. The esterification of free cholesterol into

cholesterol ester produces a more hydrophobic core, enhancing the density of the HDL particle. Another enzyme, cholesteryl ester transfer protein, mediates the transfer of cholesterol ester of the HDL, core and other circulating lipoproteins such as LDL[37].

Lipoprotein (a)

Lipoprotein (a) [LP (a)] is another lipoprotein particle which in structure is very similar to LDL with the addition of apolipoprotein (a). LP (a) links lipid metabolism with blood coagulation, [38]and because of the structural similarities of the LP (a) particle to both LDL and plasminogen, it is thought that this particle has both atherogenic and thrombogenic potential[39]. LP (a) may inhibit thrombolysis and elevated levels are linked to increased risk for coronary heart disease[40]; this risk appears greater in the presence of elevated LDL cholesterol levels.[41]

Apolipoproteins

Several apolipoprotein have been identified; Table II shows the Apolipoprotein associated with each class of lipoprotein. Apolipoprotein have many roles in lipid metabolism, which represented in Table III.

Table III

APOLIPROTEINS IN METABOLISM

APOLIPOPROTEIN (APO)	FUNCTION
ApoE (E2, E3, E4)	Responsible for mediating the uptake of remnants particles, either chylomicron remnants, VLDL, or IDL remnants
ApoB-100	Present in VLDL and LDL, acts as ligand for the LDL Receptor
ApoB-48	Found in chylomicrons and intestinal cells
ApoC (C-I,C-II,C-III)	Found on chylomicrons, VLDL and HDL particles. ApoB-II activates LPL catabolize TG. ApoC-III may inhibit action of LPL
Apo-A-I	Present in chylomicrons and HDL particles. Activated lecithin; cholesterol acyltransferase enzyme and provides structure to HDL particles
Apo-A-II	Present in chylomicrons and HDL particles. Activated hepatic triglyceride lipase.

Lipid Processing Enzymes

Table III lists several major enzymes involved in lipoprotein metabolism that have been identified. Activated by the apolipoprotein, these enzymes serve a unique role, but not all are completely understood. Table IV

TABLE IV

ENZYMES IN LIPOPROTEIN METABOLISM

ENZYME	FUNCTION
Lipoprotein lipase	Hydrolyzes TG in chylomicrons and VLDL
Lecithin-cholesterol acyltransferase	Esterifies free cholesterol on the HDL surface
Hepatic-triglyceride lipase	Hydrolyzes TG in IDL and HDL particles
Cholesterol ester transfer protein	Facilitates transfer between lipoprotein cholesterol esters and TG

LIPID GENERATION AND TRANSPORT

There are three main pathways responsible for the generation and transport of lipids within the body. These pathways include the exogenous pathway, the endogenous pathway, and the pathway of reverse cholesterol transport.[19,42]

Exogenous (Dietary) Lipid Pathway

Following digestion and absorption of dietary fat, TG and cholesterol are packaged to form chylomicrons interact at the capillaries of adipose tissue and muscle cells releasing TG to the adipose tissue to be stored and available for the body's energy needs. The enzyme LPL hydrolyzes the TG and free-fatty acids are released. Some of the components of the chylomicrons are "repackaged" into other lipoproteins, for example, some apolipoprotein are transferred to HDL, and the remaining chylomicrons remnant particles are removed from the plasma from the plasma by way of chylomicron remnant receptors present on the liver.

Endogenous Pathway

The endogenous pathway involves the liver synthesizing lipoproteins. TG and cholesterol ester are generated by the liver and packaged into VLDL particles and then released into the circulation. VLDL is then processed by LPL in tissues to release fatty acids and glycerol. The fatty acids are taken upon by muscle cells for energy or by the adipose cells for storage. Once processed by LPL, the VLDL becomes a VLDL remnant. The majority of the VLDL remnants are taken up by the liver via the LDL receptor, and the remaining remnant particles become IDL, a smaller, denser lipoprotein than VLDL. The fate of some of the IDL particles requires them to be reabsorbed by the liver (again by the LDL receptor); however other IDL particles are hydrolysed in the liver by hepatic-triglyceride lipase to form LDL, smaller, denser particle than IDL.

LDL is the main carrier of circulating cholesterol within the body, used by extra-hepatic cells for cell membranes and steroid hormone synthesis. Much of the LDL, particles are taken up by LDL, receptors in the lever, the remaining LDL, is removed by way of scavengers pathway at the cellular level. As LDL is taken up by receptors free cholesterol is releasedand accumulates within the cells. LDL receptor activity ad uptake of LDL regulate plasma LDL concentration by several mechanisms, including decreasi9ng the synthesis of hyddroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductive (which controls rate of cholesterol synthesis), suppressing the synthesis of new LDL receptors in the cells and activating the enzyme, acyl-coenzyme A cholesterol acyltransferase, which esterified free cholesterol into cholesterol ester, storing cholesterol in the cell[43].

Reverse Cholesterol Transport

Reverse Cholesterol transport refers to the process by which cholesterol is removed from the tissues and returned to the liver[44]. HDL is the key lipoprotein involved in reverse cholesterol transport and the transfer of cholesteryl esters between lipoprotein[45]. The smallest and most dense lipoprotein particle is HDL. HDL is formed through a maturation process whereby precursor particles (nascent HDL) secreted by the liver and intestine proceed through a series of conversions (known as the “HDL cycle”) to attract cholesterol from cell membranes and free cholesterol to

the core of the HDL particle. There are subclasses of HDL particles, including HDL_2 and HDL_3. The exact mechanism by which the HDL delivers cholesterol esters to the liver is not well understood, but several mechanisms have been suggested. These

include the Action of cholesteryl ester transfer protein, which transforms HDL into TG-rich particle that interacts with hepatic-triglyceride lipase. Cholesterol ester-rich HDL may also be taken up directly by the receptors in the liver. Another mechanism may be that cholesterol esters are delivered directly to the liver for uptake without catabolism of the HDL cholesterol particle[44/46].

In the context of cardiovascular disease risk, it is established that higher levels of HDL are associated with lower levels of heart disease; therefore higher levels of HDL are considered to be protective[47]. In contrast, it is now appreciated that other lipoproteins, including VLDL, IDL, LDL, andthe remnant particles rendered in lipid processing, are highly atherogenic. To reflect this, the term "non-HDL cholesterol" has been invoked to describe this increased risk reflected in the lipid profile that may not be otherwise identified by simply examining the LDL alone[48]. Non-HDL cholesterol therefore encompasses a broader indication of cardiovascular disease risk. This parameter is calculated by equation {non-HDL cholesterol=total cholesterol-HDL} and is an important consideration in ensuring that patients are treated appropriately to target levels.

LIPOPROTEIN DISORDERS[49]

There are five primary inherited lipoprotein disorders which disturb lipid metabolism at the points these are:

Familial hypertriglyceridemia (FHTG) (unknown), including lipoprotein lipase (LPL) deficiency, in which low LPL activity results in decreased removal, and thus increase of serum triglyceride; there is increased hepatic secretion and thus raised plasma concentration of triglyceride-rich VLDL. Patients are at risk of recurrent acute pancreatitis when plasma triglycerides exceed 10 mmol/l, and especially 20 mmol/l.

Familial combined hyperlipidaemia (FCHL) (common and most important) in which there is increased hepatic secretion if apolipoprotein B containing VLDL,

and conversion to LDL; in consequence plasma LDL and VLDL are raised. Patients exhibit macro vascular disease (coronary heart, peripheral and cerebral)

Remnant removal disease (RRD), also called remnant lipaemia, familial dysbetalipoproteinemia) (uncommon) in which there is a defect of apolipoprotein E. This is the major ligand that allows internalized and subsequent metabolism of remnant particles derived from VLDL and chylomicrons. The consequence is accumulation of VLDL remnant called intermediate density lipoprotein (IDL) with cholesterol and triglycerides usually in the range 6-9 mmo1/1. Patients experience severe macro vascular disease.

Familial hypoalphalipoproteinemia (rare) in which the serum concentration of (protective) HDL is low. Coronary heart and peripheralvascular disease result.

Familial hypercholesterolemia (FH) (common) is characterized by elevations of total and LDL cholesterol to plasma. In the more severe heterozygous form this affects about 1:500 of the population (one copy of the LDL-receptor protein is absent or defective). LDL-cholesterol is elevated from childhood. Untreated, half the males will be dead by 60 years, females 10 years later. The principal consequence is coronary heart, but occasionally also peripheral and cerebrovascular disease.

CONSEQUENCES OF LIPID ABNORMALITIES

Dyslipidemia is a major risk factor for atherosclerosis is a disease process that affects the coronary, cerebral and peripheral arterial circulation.

Coronary Heart Disease (CHD)[50]

The etiology of atherosclerosis is multi factorial but the cause-effect relationship between dyslipidaemia and atherosclerosis has been shown in many studies and trials.

The reducing the plasma LDL cholesterol level sharply reduces the risk of subsequent clinical CHD in both patients with pre-existing CHD and in patients free of CHD. There is no doubt about the atherogenesisi of LDL. Evidence suggests that oxidative modification of LDL within the artery is necessary for mediating its atherogenicity.

An atherogenic lipoprotein pattern. Characterised by a predominance of small dense LDL, moderately elevated plasma triglycerides and low levels is the most powerful risk factor for CAD.

Stroke[51]

Stroke is a term that describes a clinical event caused either by occasion or haemorrhage in the arterial supply to the central nervous system resulting in tissue infraction. It is one of the most distributing consequences of vascular disease. Atheroma formation is the root of pathogenesis of thromboembolic stroke. Observational studies suggested that dyslipidaemia particularly high LDL-C, low HDL-C and high TG are important risk factors for thrombi-embolic stroke.

Peripheral Artery Disease (PAD) [52]

Peripheral artery disease is most commonly a manifestation of systemic atherosclerosis in which the arterial lumen of the lower extremities becomes progressively occluded by atherosclerotic plaque. High lipoprotein concentrations are important in the development of PAD

Evidence that atherosclerosis in the peripheral circulation should be considered in the same manner as atherosclerosis in the coronary circulation. Patients with PAD, even in the absence of a history of myocardial infraction or stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with a history of coronary of cerebrovascular disease.

PATIENT RELATED RISK FACTORS[53]

Diabetes Mellitus

Premature atherosclerotic disease is the main cause of reduced life expectancy in patients with diabetes.

Type 1 Diabetes in patients with type 1 diabetes HDL-C may appear high

Type 2 Diabetes patients with type 2 diabetes typically have increased triglycerides and decreased HDL-C

Hypothyroidism

Abnormality of serum lipid and lipoprotein levels is common in patients with untreated hypothyroidism. It is an important cause of secondary dyslipidaemia.

Chronic renal failure[54]

Dyslipidemia is frequently seen in patients with renal failure in the predialysis phase, during haemodialysis or when undergoing chronic ambulatory peritoneal dialysis.

Nephrotic syndrome

Dyslipidemia appears to be caused by an increased production of apolipoprotein B-100 and associated LDL-C.

Obesity

Chronic, excessive intake of calories leads to increased concentrations of triglycerides and reduced HDL-C

Alcohol

In the heavy drinker the high caloric content of beer and wine may be a cause of obesity with its associated adverse effects on the lipid profile. In addition, alcohol increases hepatic triglycerides synthesis, which in turn produces hypertreiglyceridemia.

Drugs[55]

A number of drugs can adversely affect serum lipid and lipoprotein concentration.

Antihypertensive agents

Hypertension is a major risk factor for atherosclerosis, and the beneficial effects of lowering blood pressure are well recognized.

Diuretics

Thiamine and loop diuretics increase VLDL-C and LDL-C by mechanisms that are not completely understood

β- blockers

The effect of β- blockers on lipoprotein metabolism is reflected in an increase in serum triglycerides concentrations, a decrease in HDL-C, there is no visible effect on LDL-

Oral Contraceptives

Estrogens cause a slight increase in hepatic production of VLDL-C and HDL-C reduce serum LDL-C levels. In contrast progestogens increase LDL-C and reduce serum HDL-C and VLDL-C.

Corticosteroids

Administrations of glucocorticoids, for example prednisolone, have been shown to increase TC and triglycerides by elevating LDL-C and, less consistently, VLDL-C.

Ciclosporin

Ciclosporin is primarily used to prevent tissue rejection in recipients of renal, hepatic and cardiac transplants. Its use has been associated with increased LDL-C levels. Hepatic microsomal enzyme inducers.

Drugs such as carbamazepine, phenytoin, phenobarbital, rifampicin and griseofulvin, which increase hepatic microsomal enzyme activity, can also increase serum HDL-C. The administration of these drugs may also give rise to a slight increase in LDL-C and VLDL-C.

PATHOLOGY OF DYSLIPIDEMIA

Dyslipidemia "refers to an abnormality within the lipid profile, encompassing a variety of disorders relating to elevations in total cholesterol, LDL, or TG, or conversely, lower levels of HDL. The dyslipidemia may present as a single disorder

affecting only one lipoprotein parameter, or may represent a combination of lipoprotein abnormalities, such as elevated TG and low HDL.

A dyslipidemia may be the result of over-production or lack of clearance of the lipoprotein particles, or related to other defects in the apolipoprotein or enzyme deficiencies. The pathway and means of lipid metabolism in the human body reflect complex processes, and genetics, certain medical conditions, medications, and/or environmental factors may influence lipoprotein metabolism in some capacity, resulting in a dyslipidemic condition. In the clinical setting, a primary dyslipidemia typically refers to a genetic defect in the lipid metabolism as a cause of the problem[36].

A secondary dyslipidemia may be attributed to another cause. For example, environmental factors (such as a diet rich in saturated fat or a sedentary lifestyle), diseases (such as diabetes, hypothyroidism, obstructive liver disease), and medications (such as thiazide diuretics, progestins, or anabolic steroids) may result in a secondary dyslipidemia[57'58].

CLINICAL PRESENTATION

General

- Most patients are asymptomatic for many years prior to clinically evident disease.
- Patients with the metabolic syndrome may have three or more of the following: abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance with or without glucose intolerance, prothrombotic state, or protinflammatory state.

Symptoms

- None to chest pain, palpitations, sweating, anxiety, shortness of breath, loss of consciousness or difficulty with speech or movement, abdominal pain, and sudden death.

Signs

- None to abdominal pain, pancreatitis, eruptive Xanthomas, peripheral polyneuropathy, high blood pressure, body mass index greater than 30 kg/m2, or waist size greater than 40 inches in men (35 inches in women).

Laboratory tests

- Elevations in total cholesterol, LDL, triglycerides, apolipoprotein B, and C-reactive protein.
- Low HDL.

Other diagnostic test

- Lipoprotein (a), homocysteine, serum amyloid A, and small, dense LDL (pattern B).
- Various screening test for manifestations of vascular disease (ankle-brachial index, exercise testing, and magnetic resonance imaging) and diabetes (fasting glucose, oral glucose tolerance test).

MANAGEMENT OF DYSLIPIDEMIA

The current NCEP guidelines for management of patients are of two types. One is a population-based approach to reduce CHD risk, which includes recommendations to increase exercises (to expend-2000 calories/week) and to lower blood cholesterol by dietary recommendations: reduce total calories from fat to less than 30% and from saturated and trans fats to less than 10%; consume less than 300mg of cholesterol per day; eat a variety of oily fish twice a week[59] and oils/foods rich in linoleic acid (canola, flaxseed and soybean oils, flaxseed and walnuts); and maintain desirable body weight. The second is the patient0based approach that focuses on lowering LDL-C levels as the primary goal of therapy[60]

The guidelines for the management of adults 20 years and older recommended a complete fasting lipoprotein profile (total cholesterol, LDL-C, HDL-C, and triglycerides). The classification of lipid levels is shown in (Table V).

TABLE-V

CLASSIFICATION OF PLASMA LIPID LEVELS

Test	**Normal Values**	
Serum Cholesterol	American Heart Association recommendation	Normal up to 200 mgs/dl
	Borderline	Up to 239 mgs/dl
	Elevated if>240 mgs/dl. On repeated values	
Serum Triglycerides	<180 mgs/dl. Normal. Values vary depending on diet, alcohol, metabolic state, exercise etc. Elevation of values to be considered only if repeated values are high.	
HDL Cholesterol	30-60 mgs/dl	
LDL Cholesterol	100-190 mgs/dl	Borderline
	>190 mgs/dl	Risk
	Formula for calculating LDL Cholesterol is INVALID if TGL>400 mgs/dl	
Total/HDL ratio	<4	Normal
	4-6	Low Risk
	>6	High Risk

If the values or total cholesterol, LDL-C, and triglycerides are in the lowest category and the HDL-C level is not low, lifestyle recommendations (diet and exercise) should be made to ensure maintenance of a normal lipid profile. Other vascular disease risk factors (Table VIII), if present should be assessed and treated individually. For patient with elevated levels of total cholesterol, LDL-C, or triglycerides, or reduced HDL-C values, further treatment is based on the patient's risk-factor status (Table VIII), and calculation of the Framingham risk score (Table of primary prevention patients with two or more risk factors.

TABLE VI

Risk Factors for Coronary Heart Disease

Age	Male >45 years or female > 55 years
Family history of premature CHD	A first-degree relative (male below 55 years or female below 65 years when the first CHD clinical event occurs
Current cigarettes smoking	Defined as smoking within the preceding 30 days
Hypertension	Blood pressure = 140/90 or use of antihypertensive medication, irrespective of blood pressure
Low HDL-C	<40 mg/dl (consider <50mg/dl as "low" for women)
Obesity	Body mass index > 25 kg/m² and waist circumference above 40 inches (men) or 35 inches (Women)

All patients who meet the criteria for lipid-lowering therapy should receive instruction about therapeutic lifestyle change. Dietary restrictions include less than 7% of calories from saturated and trans fatty acids, less than 200 mg of cholesterol daily, up to 20% of calories from monounsaturated fatty acids, up to 10% of calories from polyunsaturated fat, and total fat calories ranging between 25% and 35% of all calories. Two oily fish meals per week are especially important for post-myocardial infraction patients due to a substantial reduction in the risk of sudden cardiac death. Patients with CHD or a CHD equivalent (symptomatic peripheral or carotid vascular disease, abdominal aortic aneurysm, 20% 10-year CHD risk, or diabetes mellitus) should immediately start appropriate lipid-lowering drug therapy irrespective of their baseline LDL-C level[61]. Patients without CHD or CHD equivalent should be managed with lifestyle advice (diet, exercise, weight management) for 3 to 6 months before drug therapy is implemented.

Risk Assessment Using Framingham Risk Scores[62]

The 2001 NCEP guidelines and those of the European Atherosclerosis Society employ risk assessment tables devised from the Framingham Heart study in an attempt to match the intensity of treatment to the severity of CHD risk in patients without a prior history of symptomatic atherosclerotic vascular disease. High risk or "CHD equivalent" status is defined as >20% chance of sustaining a CHD event in the next 10 years. The tables used to determine a patient's absolute risk do not take in to account risk associated with a family history of premature CHD or obesity. As a consequence, the risk may be seriously underestimated, resulting in insufficiently aggressive management[63]. After calculation of the risk score, more aggressive therapy should be considered for obese patient with family history of premature CHD. It is also unlikely that the Framinghamrisks model is appropriate for assessing risk in all ethnic groups.

Arterial Wall Biology Plaque Stability

More effective lipid-lowering agents and a better understanding of atherogenesisi have helped to prove that aggressive lipid-lowering therapy has many beneficial effects over and above those obtained by simply decreasing lipid deposition in the arterial wall. Arterigraohic trails have shown that, although aggressive lipid lowering results only in very small increases in lumen diameter, it promptly decreases acute coronary events. Lesions causing less than 60% occlusion are responsible for more than two-thirds of the acute events through its positive effects on the arterial wall; it corrects endothelial dysfunction, corrects abnormal vascular reactivity(spasm), and increases plaque stability[64].

Atherosclerotic lesions containing a large lipid core, large numbers of macrophages, and a poorly formed fibrous cap are prone to plaque rupture and acute thrombosis. Aggressive lipid lowering appears to alter plaque architecture. Resulting in fewer lipids, less macrophages, and a larger collagen and smooth muscle cell-rich fibrous cap. Stabilization of plaque susceptibility to thrombosis appears to be a direct result of LDL-C lowering or an indirect result of changes in cholesterol and lipoprotein metabolism or arterial wall biology[65,66].

Gender

Both men and Women benefit from lipid-lowering therapy. Stains, rather than hormone-replacement therapy, are now the recommended first-line drug therapy for lowering lipids in postmenopausal women. This recommendation reflects the increased CHD morbidity in older women with established CHD who were treated with hormone-replacement therapy[67].

Age

Age >45 years in men and >55 years in women is considered to be a CHD risk factor. The stain trials have shown that patients >65 of age benefit from therapy as much as do younger patients[68].

Cerebrovascular Disease Patients:

In most observational studies, plasma cholesterol levels correlate positively with the risk of ischemic stroke. In clinical trials, statins reduced stroke and transient ischemic attacks in patients with and without CHD[69].

Peripheral Vascular Disease Patients:

Stains are beneficial in patients with peripheral vascular disease[69].

Hypertensive Patients and smokers:

The risk reduction for coronary events in hypertensive patients and in smokers is similar to that in subject without these risk factors[70].

Type 2 Diabetes Mellitus:

Patients with type 2 diabetes benefit very significantly from aggressive lipid lowering[69].

Post-Myocardial Infraction or Revascularization Patients:

A soon as CHD is diagnosed, it is essential to begin lipid-lowering therapy (NCEP guidelines: LDL-C goal <70 mg/dl for very high-risk patients. Compliance with drug therapy is greatly enhanced if treatment is initiated in the hospital[71]. It remains to be determined if stain therapy alters restenosis after angioplasty; however,

the NHLBI Post Coronary Artery Bypass Graft trail showed that statin therapy improved the long-term outcome after bypass surgery and that the lower the LDL-C, the better[72].

Low Cholesterol levels

Observational studies initially were confusing. In the United States and western Europe, low cholesterol levels were associated with an increase in noncardiac mortality from chronic pulmonary disease, chronic liver disease, cancer (many primary sites), and haemorrhagic stroke. However, more recent data indicate that it is the noncardiac diseases that cause the low plasma cholesterol levels and not the low cholesterol levels that cause the noncardiac diseases. Once exception may be haemorrhagic stroke. In the Multiple Risk Factor Intervention Trial (MRFIT), haemorrhagic stroke occurred more frequently in hypertensive patients with total cholesterol levels below 1460 mg/dl; however, the increased incidence of haemorrhagicstroke was more than offset by reduced CHD risk due to the low cholesterol were not associated with increases in haemorrhagic stroke or any other cause of noncardiac mortality[74].

A betalipoproteinemia and hypo betalipoproteinemia, two rare disorders associated with extremely low total cholesterol levels, are instructive because affected individuals have reduced CHD risk and no increase in noncardiac mortality. Patients who are homozygous for the mutations that cause these disorders have total cholesterol levels below 50 mg/dl and triglyceride levels below 25 mg/dl[75].

Individuals consuming very low levels of total fat (less than 5% of total calories) and vegetarians, who consume no animal fat, usually have total cholesterol levels below 150 mg/dl have no increase in noncardiac mortality.

Based on the lack of harm associated with low total cholesterol levels in these various groups, reducing cholesterol levels to similarly tow levels with drugs does not appear to be contraindicated. With the advent of more efficacious cholesterol-lowering agents, it soon may be possible to test the benefits and risks of lowering total cholesterol levels below 150 mg/dl. Whether even lower cholesterol levels will translate in to a further reduction in clinical events is not known, but many researchers are optimistic[76].

Diabetic dyslipidemia

Diabetes mellitus is an independent predictor of high risk for CHD. CHD morbidity is two to four times higher in patients with diabetes than in nondiabetics, and themortality from CHD is up to 100% higher in diabetic patients over a 6-year period. Glucose control is essential but provides only minimal benefit with respect to CHD prevention. Aggressive treatment of diabetic's dyslipidemia through diet, weight control, and drugs is critical in reducing risk[77].

Diabetic dyslipidemia is usually characterized by high triglycerides, low HDL-C, and moderate elevations of total cholesterol and LDL-C. In fact, diabetes without diagnosed CHD has the same level of risk as nondiabetics with established CHD[78]. Thus, the dyslipidemia treatment guidelines for diabetic patients are the same as for patients with CHD, irrespective of whether the diabetic patient has had a CHD event. The first line of treatment for diabetic dyslipidemia usually should be a statin[79].

Metabolic Syndrome

There is an increased CHD risk associated with their insulin-resistant, prediabetic state described under the rubric of "metabolic syndrome". The prevalence of metabolic syndrome among patients with premature vascular disease may be as high as 50%

Treatment should focus on weight loss and increased physical activity. Since being overweight or obese usually precludes optimal risk factor reduction. Specific treatment of increased LDL-C and triglyceride levels HDL-C levels should also be undertaken[80].

Hypertrigly ceridemia

There is increased CHD risk associated with the presence of triglyceride levels above 150 mg/dl. The treatment is recommended based on the degree of elevation. Weight loss, increased exercise, and alcohol restriction are important for all hypertriglyceridemic patients. If triglycerides remain above 200 mg/dl after the LDL-C goal is reached, further reduction in triglycerides may be achieved but increasing the dose of a statin or of niacin. Combination therapy (statin plus niacin or statin plus

fibrate) may be required, but caution is necessary with these combinations to avoid myopathy[81]. .

Low HDL cholesterol.

Low HDL is a strong independent risk predictor of CHD. The ATP III redefined low HDL cholesterol as less than 40 mg/dL but specified no goal for HDL cholesterol raising[82]. Low HDL may be a consequence of insulin resistance, physical inactivity, type 2 diabetes, cigarettes smoking, very high carbohydrate intake, and certain drugs[83]. In low HDL, the primary target remains LDL according to the ATP III, but emphasis shifts to weight reduction, increased physical activity, and smoking cessation and, if drug therapy is required, to fabric acid derivatives and niacin. Niacin has the potential for the greatest increase in HDL, and the effect is more pronounced with regular or immediate0release forms than with sustained-release forms[84]

TABLE VII

HYPOLIPIDEMIC DRUGS

Drugs	**Lipoprotein class affected**	**Common side effects**	**Contraindications**
HMG-CoA reductase inhibitors Lovastatin 20-80 mg/d Pravastatin 40-80 mg qhs Simvastatin 20-80 mg qhs Fluvastatin 20-80 mg qhs Atorvastatin 10-80 mg qhs Resuvastatin 10-40 mg qhs	↑LDL 25-55% ↑TG 10-20% ↑HDL 5-10%	Myalgias, Arthralgias, Transaminases, dyspepsia	Acute or chornic liver disease of myositis increased by impaired renal function and in combination with a fibrate
Nicotinic acid	↑LDL 15-25% ↑TG 25-35% ↑HDL 15-30%	Flushing(may be relieved by aspirin), hepatic dysfunction, nausea, diarrhea, glucose intolerance, hyperuricemia	Peptic ulcer disease, hepatic disease, gout
Fish oils 3-12g qd	↑TG 5-10%	Dyspepsia, diarrhea, fishy odor to breath	
Cholesterol absorption inhibitors Ezetimibe 10 mg qd	↑LDL 18% ↑TG 8%	Transaminases	
Bile acideswquestrant Cholestyramine 4-32 g qd Cholestipol 5-40 g qd Colesevelam 3750-4375 mg qd Fibric acid derivaties Gemfibrozil 600 mg bid Fenofibrate 160 mg qd Immediate release 100mg tid. Gradual increase to 2gtid Sustained release 250 mg- 1.5 g bid Extended released 500 mg-2 g qhs	↑LDL 20-30% ↑TG 10% ↑HDL 5% ↑or↓ LDL ↓TG 25-40% ↓HDL 5-15%	Constipation, gastric discomfort, nausea Absorption of other drugs Gallstones, dyspepsia, hepatic dysfunction, Myalgia	Biliary tract obstruction, gastric outlet obstruction Hepatic or biliary disease, renal insufficiency associated with↑ risk of myositis

Statins

The statins are the most effective and best-tolerated agents for treating dyslipidaemia. These drugs are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyses an early, rate-limiting step in cholesterol biosynthesis,. Higher doses of the more potent statin (e.g., atorvastatin and simvastatin) also can reduce triglyceride levels caused by elevated VLDL levels. Some statins also are indicated for raising HDL-C levels, although the clinical significance of these effects on HDL-C remains to be proven[85].

History

Statins were isolated from a shape, Penicillin citrinum, and identified as inhibitors of cholesterol biosynthesis in 1976 by Endo and colleagues. Subsequent studies by Brown and Goldstein established that statins act by inhibiting HMG-CoA reductase. The first statin studied in humans was compacting, renamed mevastatin, which demonstrated the theraptic potential of this class of drugs. However, albert and colleagues at Merck developed the first statin approved for use in humans, lovastatin (formerly known as mevinolin), which was isolated from Aspergillums terreus. Five other statins are also available. Pravastatin and simvastatin are chemically modified derivatives of lovastatin. Atorvastatin, fluvastatin, and rosuvastatin are structurally distinct synthetic compounds[86].

Mechanism of Action

Statins exert their major effect reduction of LDL levels through a mevolonic acid-like moiety that competitively inhibits HMG-CoA reductase. By reducing the conversion of HMG-CoA to mevalonate, statins inhibit an early and rate-limiting step in cholesterol biosynthesis[87].

Bile-Acid sequestrants

The two established bile-acid sequestrants orresins (cholestyramine and colestipol) are among the oldest of the hypolipidemic drugs, and they are probably the safest, since they are not absorbed from the intestine. These resins are also recommended for patients 11 to 20 years of age. Because statins are so effective as monotherapy, the resins are most often used as second agents if statin, therapy does

not lower LDL-C levels sufficiently. When used with a statin, cholestyramine and colestipol usually are prescribed at submaximal doses. Maximal doses can reduce LDL-C by up to 25% but are associated with unacceptable gastrointestinal side effects (bloating and constipation) that limit compliance[88].

Niacin (Nicotinic Acid)

The hypolipidemic effects of niacin require larger doses than are required for its vitamin effects. Niacin is the best agent available for increasing HDL-C (increments of 30% to 40%); it also lowers triglycerides by 35% to 45 % (as effectively as fibrates and the more potent statins) and reduces LDL-C levels by 20% to 30%.[89]

Fibric Acid Derivatives: PPAR Activators

Total mortality was significantly greater in the clofibrate group. The increased mortality was due to multiple causes, including cholelithiasis. Interpretation of these negative results was clouded by failure to analyse the data according to the intention-to-treat principle. A later analysis demonstrated that the apparent increase in noncardiac mortality did not persist in the clofibrate-treated patients after discontinuation of the drug[90].

Ezetimibe and the Inhibition of Dietary Cholesterol uptake

Ezetimibe is the first compound approved for lowering total and LDL-C levels that inhibits cholesterol absorption by enterocytes in the small intestine. It lowers LDL-C levels by about 18% and is used primarily as adjunctive therapy with statins. Outcome studies employing Ezetimibe with statins are beginning, but no result are anticipated for several years[91].

CHAPTER III

DROUG PROFILE

3. DRUG PROFILE

Atorvastatin calcium

DESCRIPTION

Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

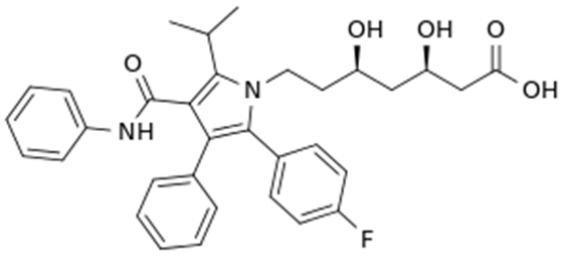
Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

CHEMICAL NAME

Atorvastatin calcium is [R-(R*, R*)]-2-(4-flurophenyl), β, d-dihydroxy-5-(1-methylethyl) -3- phenyl- 4- [(phenyl amino) carbonyl]-1Hpyrrole-1- heptanoicacid, Calcium salt (2:1) trihydrate.

Molecular Weight is 1209.42.

Structural formula is:



Empirical Formula $(C_{33}H_{34}FN_2O_5)2Ca.3H_2O)$

CLINICAL PHARMACOLOGY

Mechanism of action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3 methylglutray1-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL- cholesterol (LDL-C), and apolipoprotein B (ApoB) promote human atherosclerosis and are risk factors for developing cardiovascular disease.

Pharmacokinetics and drug metabolism

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to Atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution

Mean volume of distribution of Atorvastatin is approximately 381 litres. Atorvastatin IS >-98% bound to plasma proteins. A blood/plasma ration of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of Atorvastatin. Approximately 70% of circulating inhi9bitroy activity for HMG-CoA reductase is attributed to active metabolites.

Excretion

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of Atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory active metabolites. Less than 2% of a dose of Atorvastatin is recovered in urine following oral administration.

Indication & dosage

Adjunct to diet to reduce elevated LDL, total cholesterol, apo B and triglycerides levels in patients with primary hypercholesterolemia and mixed dyslipidemia.

Adults

Hyperlipidemia: Initial: 10-20 mg once daily; patients requiring >45% reduction in LDL-C may be started at 40 mg once daily; range: 10-80 mg once daily

Primary prevention of CVD: 10 mg once daily

Dosage Forms:

Tablet: 10 mg, 20 mg, 40 mg, 80 mg

Contraindications & precaution

Contraindicated in patients hypersensitive to drug with active hepatic disease or conditions associated with unexplained persistent elevations of serum traniminaselevels,in pregnant or feeding women and in women of child bearing. Use cautiously in patients with history of hepatic disorder heavy alcohol use.

Special Populations

Geriatric

Plasma concentrations of Atorvastatin (Atorvastatin) are higher (approximately 40 % for Cmax and 30% for AUC) in healthy elderly subjects (age 65 years) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Atorvastatin (Atorvastatin).

Paediatric: Pharmacokinetic data in the paediatric population are not available.

Gender :

Plasma concentrations of Atorvastatin (Atorvastatin) in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Atorvastatin (Atorvastatin) between men and Women.

Renal Insufficiency:

Renal disease has no influence on the plasma concentrations or LDL-C reduction of Atorvastatin (Atorvastatin); thus, dose adjustment in patients with renal dysfunction is not necessary.

Hemodialysis:

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of Atorvastatin (Atorvastatin) since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency:

In patients with chronic alcoholic liver disease, plasma concentrations of Atorvastatin are markedly increased.

Drug Interactions: Substrate of CYP3A4 (major); Inhibits CYP3A4 (weak)Antacids: Plasma concentrations may be decreased when given with magnesium-aluminium hydroxide containing antacids (reported with atorvastatin and pravastatin). Clinical efficacy is not altered, no dosage adjustment is necessary.

Cholestyramine and colestipol (bile acid sequestrants): Reduce absorption of several HMG-CoA reductase inhibitors; separate administration times by at least 4 hours. Cholesterol-lowering effects are additive.

Clofibrate and fenofibrate may increase the risk of myopathy and rhabdomyolysis. CYP3A4 Inhibitors: May increase the levels/effects of atorvastatin. Example inhibitors include azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, /nefazodone, nicardipine, propofol, protease inhibitors, quinidine, and verapamil.

Digoxin: Plasma concentrations of digoxin may be increased by 20%.

Grapefruit juice: May inhibit metabolism of atorvastatin via CYP3A4; more likely to occur with lovastatin or simvastatin; avoid high dietary intake of grapefruit juice. Niacin may increase the risk of myopathy and rhabdomyolysis.

Adverse Reactions

Central nervous system: Insomnia, dizziness, headache

Cardiovascular: Chest pain, peripheral edemas

Dermatologic: Rash (1% to 4%)

Gastrointestinal: Abdominal pain (up to 4%), constipation (up to 3%), diarrhoea (up to 4%), dyspepsia (1% to 3%), flatulence (1% to 3%), nausea

Genitourinary: Urinary tract infection

Hepatic: Transaminases increased (2% to 3% with 80 mg/day dosing)

Neuromuscular & skeletal: Arthralgia (up to 5%), arthritis, back pain (up to 4%), myalgia (up to 6%). Weakness (up to 4%)

Respiratory: Sinusitis (up to 6%), pharyngitis (up to 3%), bronchitis, rhinitis

Miscellaneous: Infection (3% to 10%), flu-like syndrome (up to 3%), allergic reaction (up to 3%)

3. DRUG PROFILE-II

PITAVASTATIN CALCIUM

DESCRIPTION

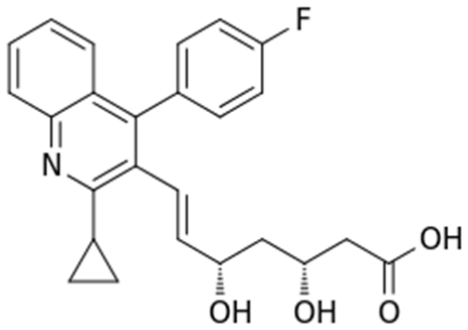
Pitavastatin (usually as a calcium salt) is a member of the blood cholesterol lowering medication class of statins. Like other statins, it is an inhibitor of HMG-CoA reductase, the enzyme that catalyses the first step of cholesterol synthesis.

CHEMICAL NAME

(3*R*, 5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxyhept-6-enoic acid

Molecular Weight: 421.461

STRUCTURAL FORMULA:



Empirical formula: $\mathbf{C_{25}H_{24}FNO_4}$

CLINICAL PHARMACOLOGY

Mechanism of Action

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis ofcholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, theexpression of LDL-receptors followed by the uptake of LDL from blood to

liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins.

Pharmacodynamics

In a randomized, double-blind, placebo-controlled, 4-way parallel, active-comparator study with moxifloxacin in 174 healthyparticipants, Pitavastatin was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to16 mg (4 times the recommended maximum daily dose).

Pharmacokinetics

Absorption: Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both Cmax and AUC0-inf increased in an approximately dose-proportional manner for single Pitavastatin doses from 1 to 24 mg once daily. The absolutebioavailability of Pitavastatin oral solution is 51%. Administration of Pitavastatin with a high fat meal (50% fat content) decreases pitavastatin Cmax by 43% but does not significantly reduce Pitavastatin AUC. The Cmax and AUC of pitavastatin did not differfollowing evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the per cent change from baselinefor LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the smallintestine but very little in the colon.

Distribution: Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, andthe mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells isminimal.

Metabolism: Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite inhuman plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uredines 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion: A mean of 15% of radioactivity of orally administered, single 32 mg 14C-labeled pitavastatin dose was excreted in urine,whereas a mean of 79% of the dose was excreted in faces within 7 days. The mean plasma elimination half-life is approximately 12hours.

Race: In pharmacokinetic studies pitavastatin Cmax and AUC were 21 and 5% lower, respectively in Black or African Americanhealthy volunteers compared with those of Caucasian healthy volunteers. In pharmacokinetic comparison between Caucasianvolunteers and Japanese volunteers, there were no significant differences in Cmax and AUC.

Gender: In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin Cmax and AUC were 60 and54% higher, respectively in females. This had no effect on the efficacy or safety of Pitavastatin in women in clinical studies.

Geriatric: In a pharmacokinetic study which compared healthy young and elderly (65 years) volunteers, pitavastatin Cmax and AUCwere 10 and 30% higher, respectively, in the elderly. This had no effect on the efficacy or safety of Pitavastatin in elderly subjects inclinical studies.

Renal Impairment: In patients with moderate renal impairment (glomerular filtration rate of 30 – 59 mL/min/1.73 m2) and end stagerenal disease receiving hemodialysis, pitavastatin AUC0-inf is 102 and 86% higher than those of healthy volunteers, respectively, whilepitavastatin Cmax is 60 and 40% higher than those of healthy volunteers, respectively. Patients received hemodialysis immediatelybefore pitavastatin dosing and did not undergo hemodialysis during the pharmacokinetic study. Hemodialysis patients have 33 and36% increases in the mean unbound fraction of Pitavastatin as compared to healthy volunteers and patients with moderate renalimpairment, respectively.

In another pharmacokinetic study, patients with severe renal impairment (glomerular filtration rate 15 – 29 mL/min/1.73 m2) notreceiving hemodialysis were administered a single dose of Pitavastatin 4 mg. The AUC0-inf and the Cmax were 36

and 18% higher, respectively, compared with those of healthy volunteers. For both patients with severe renal impairment and healthy volunteers, themean percentage of protein-unbound Pitavastatin was approximately 0.6%. The effect of mild renal impairment on Pitavastatin exposure has not been studied.

Hepatic Impairment: The disposition of Pitavastatin was compared in healthy volunteers and patients with various degrees of hepaticimpairment. The ratio of Pitavastatin Cmax between patients with moderate hepatic impairment (Child-Pugh B disease) and healthyvolunteers was 2.7. The ratio of Pitavastatin AUCinf between patients with moderate hepatic impairment and healthy volunteer's was 3.8. The ratio of Pitavastatin Cmax between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteer's was 1.3. The ratio of Pitavastatin AUCinf between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean Pitavastatint½ for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively.

Drug-Drug Interactions: The principal route of Pitavastatin metabolism is glucuronidation via liver UGTs with subsequent formationof Pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system.

Warfarin: The steady-state pharmacodynamics (international normalized ratio [INR] and prothrombin time [PT]) andpharmacokinetics of warfarin in healthy volunteers were unaffected by the co-administration of Pitavastatin 4 mg daily. However,patients receiving warfarin should have their PT time or INR monitored when pitavastatin is added to their therapy.

Indications and usage

Pitavastatin is a HMG-CoA reductase inhibitor indicated for:

• Patients with primary hyperlipidaemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), lowdensity lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C)

Contraindications

- Known hypersensitivity to product components
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
- Women who are pregnant or may become pregnant.
- Nursing mothers.
- Co-administration with cyclosporine.

Dosage and Administration

Pitavastatin can be taken with or without food, at any time of day Dose Range: 1 mg to 4 mg once daily.

Primary hyperlipidaemia and mixed dyslipidemia: Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day.

Moderate and severe renal impairment (glomerular filtration rate 30 – 59 and 15 - 29 mL/min/1.73 m2, respectively) as well as end-stage renal disease on hemodialysis: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily.

Special Populations

Paediatric use: Safety and effectiveness have not been established. Renal impairment: Limitation of a starting dose of Pitavastatin 1 mg once daily and a maximum dose of Pitavastatin 2 mg once daily for patients with moderate and severe renal impairment as well as patients receiving hemodialysis.

Drug Interactions

Erythromycin: Combination increases pitavastatin exposure. Limit pitavastatin to 1 mg once daily

Rifampin: Combination increases pitavastatin exposure. Limit pitavastatin to 2 mg once daily

Concomitant lipid-lowering therapies: Use with fibrates or lipidmodifying doses (³1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with pitavastatin. Store at room temperature between 15°C and 30°C (59° to 86° F). Protect from light.

CHAPTER IV

REVIEW OF LITERATURE

4. REVIEW OF LITREATURE

In a study **Calhoun, ET at**[92]we examined whether atorvastatin affects diabetic kidney disease and whether the effect of atorvastatin on cardiovascular disease (CVD) varies by kidney status in patients with diabetes. A modest beneficial effect of atorvastatin on egger, particularly in those with albuminuria, was observed. Atorvastatin did not influence albuminuria incidence. Atorvastatin was effective at decreasing CVD in those with and without a moderately decreased eGFR and achieved a high absolute benefit.

In a study performed **Area ET al**[93]**.** FCHL showed lower serum adiponectin levels compared to controls. Also normalipaemic relatives of FCHL patients presented decreased levels of adiponectin, suggesting a possible common back ground in the determination of this abnormality. Overall, these observations indicate that hypoadiponectinemia may be and inherent characteristics of the FCHL phenotype. In FCHL Patient's hypoadiponectinemia may be partially corrected by atorvastatin but not be fenofibrate treatment.

Cemil Kaya, ET al[94]**.** Patients were randomly divided into groups for treatment: group 1, atorvastatin, and 20 mg daily (n ¼ 26), and group 2, simvastatin, 20 mg daily (n ¼ 26). Blood samples were obtained before and after treatment. After 12 weeks of treatment, serum homocysteine levels in group 1 have decreased from 14.3 ± 2.9 to 10.6 ± 1.7 mmol/L; in group 2, the levels decreased from 13.6 ± 2.1 to 11.1 ± 1.9 mmol/L. Both two groups, free testosterone and total testosterone declined statistically significantly (38.3% and 36.5 %; and 40.6% and 46.0%, respectively). In group 1, vitamin B12 increased from 362.1±107 to 478.7 ± 267 pg. /mL; in group 2, it increased from 391.3 ± 107 to 466 ± 211 pg. /mol, but the change did not reach statistical significance. There was a considerable decline in the homeostatic model assessment index in group 1 (40.0% to 32.1 %). Treatment with statins in women with PCOS leads to decreased in serum homocysteine levels.(Fetril Steril -2009; 92:635-42. 2009 by American Society for Reproductive Medicine.)

Morteza Enajat, et al[95]. in the study shows that intensive cholesterol lowering therapy with a combination of atorvastatin 40 mg/day and Ezetimibe 10 mg/day in elderly AF patients receiving standard vitamin K –dependent OAC therapy targeting INR levels of 2.5-3.5 leads to minimal, but statistically significant, OAC therapy dose modifications only During the first 3 months. No serous bleeding disorders occurred during a follow-up of 12 months. The findings of this pilot study support the inclusive of elderly patients with AF receiving long-term OAC treatment in large trails investigating the beneficial effect of intensive cholesterol- lowering therapy.

Nakarin Sansanayudh, ET al[96]. Pitavastatin lowered LDL-C levels from baseline by 37% compared with 46% in the atorvastatin group ($p < 0.001$). The reduction of total cholesterol (TC) levels from baseline was significantly different between the pitavastatin (28%) and atorvastatin (32%) groups ($p = 0.005$). There was no significant difference in the percentage of changes in triglyceride and high-density lipoprotein cholesterol levels between groups. The percentage of patients who achieved LDL-C goals according to National Cholesterol Education Program–Adult Treatment Panel III guidelines was not significantly different between the pitavastatin (74%) and atorvastatin (84%) groups ($p = 0.220$). In addition, both regimens were well tolerated, with no patient developing an elevation of more than 3 times the upper normal limit of alanine aminotransferase or 10 times that of creatine kinase. The monthly cost per percent LDL-C reduction in the pitavastatin group ($0.77) was about 50% lower than the cost in the Atorvastatin ($1.56) group.

Mir Abolfazl Ostad et al[97]. the results of our study demonstrate important effects of atorvastatin, independent of LDL-Cholesterol reduction, on the vasodilatory capacity in patients with CAD in a randomizes trail. These effects mainly affect the endothelium but may also extent to protective structural changes of the vascular wall. Thus, our data argue against the concept that combination of low dose statin with Ezetimibe may replace high dose statin therapy for secondary prevention in patients with atherosclerosis.

Peter S. Sever ET al[98]. 19.342 hypertensive patients were randomised to either an amlodipine or an atenolol – based regimen in the ASCOT Blood Pressure – Lowering Arm (BPLA). 10.305 subjects with total cholesterol $\leq$6.5 mmol/L were

further randomised to atorvastatin 10 mg or placebo in the Lipid- Lowering Arm (LLA). CHD benefits associated with BP and lipid lowering were larger than predicted by pervious observation and trail data. We estimate that compared with pre-trail treatment, treating about 55 patients with the amlodipine – based regimen and atorvastatin would prevent One CHD event per year.

Robinson ET al[99]. The present double – blind, randomized, 6 week study assessed the lipid-lowering efficacy of Ezetimibe/simvastatin 10/20mg versus atorvastatin 10 or 20 mg, and Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in 1.128 patients with hypercholesterolemia and the metabolic syndrome. Ezetimibe/simvastatin was more likely to results in lipid treatment end points than atorvastatin and was generally well tolerated at the doses compared in our patients.

Alexander E. Fraley ET al[100]. This study measured OxPL/apoB, lipoprotein (a) [Lp(a)], and oxidized low-density lipoprotein (OxLDL) biomarkers, consisting of immunoglobulin IgG and IgM autoantibodies to malondialdehyde (MDA) –low-density lipoprotein (LDL) and IgG and IgM apoB-100 immune complexes (IC/apoB), at baseline and after 16 weeks of treatment with atorvastatin 80 mg/day or placebo in 2,342 patients with acute coronary syndromes (ACS) enrolled in the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trail. Atorvastatin uniformly increased OxPL/apoB levels in all subgroups studied. Future studies are warranted to assess whether the increase in OxPL/apoB levels reflects the benefit of effective therapeutic interventions and prediction of new CVD events.

Yoko K, ET al[101]. The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor pitavastatin suppressed basal and cytokine-treated EL expression in endothelial cells. Concomitant treatment with mevalonate or geranylgeranyl pyrophosphate completely reversed the inhibitory effect of pitavastatin, suggesting that geranylgeranylated proteins are involved in the inhibition of EL expression by statins. Inhibition of RhoA activity by overexpression of a dominant-negative mutant of RhoA or a Rho kinase inhibitor decreased EL levels. Pitavastatin reduced phospholipase activities of endothelial cells, and concomitant treatment with mevalonate reversed its inhibitory effect. Pitavastatin reduced RhoA activity and EL expression in mouse tissues. Furthermore, plasma EL concentrations in human subjects were measured by enzyme-linked immunosorbent assays. Plasma EL levels

were negatively associated with plasma HDL levels in 237 patients with cardiovascular diseases, and pitavastatin treatment reduced plasma EL levels and increased HDL-C levels in 48 patients with hypercholesterolaemia.

Miyuki Y, ET al[1O2]. Both statins and peroxisome proliferator-activated receptor (PPAR)_ ligands have been reported to protect against the progression of atherosclerosis. In the present study, we investigated the effects of statins on PPAR_activation in macrophages. Statins increased PPAR_ activity, which was inhibited by mevalonate, farnesylpyrophosphate, or geranyl pyrophosphate. Furthermore, a farnesyl transferase inhibitor and a geranyl transferase inhibitor mimicked the effects of statins. Statins inhibited the membrane translocations of Ras, RhoA, Rac, and Cdc42, and overexpression of dominant-negative mutants of RhoA (DN-RhoA) and Cdc42 (DN-Cdc42), but not of Ras or Rac, increased PPAR_ activity. Statins induced extracellular signal-regulated kinase (ERK)1/2 and p38 mitogen-activated.

Protein kinase (MAPK) activation. However, DN-RhoA and DN-Cdc42 activated p38 MAPK, but not ERK1/2. ERK1/2- or p38 MAPK–specific inhibitors abrogated statin-induced PPAR_ activation. Statins induced cyclooxygenase (COX)-2 expression and increased intracellular 15-deoxy-_12,14-prostaglandin J2 (15d-PGJ2) levels through ERK1/2- and p38 MAPK–dependent pathways, and inhibitors or small interfering RNA of COX-2 inhibited statin-induced PPAR_activation. Statins also activate PPAR_ via COX-2–dependent increases in 15d-PGJ2 levels. We further demonstrated that statins inhibited lipopolysaccharide-induced tumor necrosis factor _ or monocyte chemoattractant protein-1 mRNA expression, and these effects by statins were abrogated by the PPAR_ antagonist T0070907 or by small interfering RNA of PPAR_ or PPAR_. Statins also induced ATP-binding cassette protein A1 or CD36 mRNA expression, and these effects were suppressed by small interfering RNAs of PPAR_ or PPAR_. In conclusion, statins induce COX-2– dependent increase in 15d-PGJ2 level through a RhoA- and Cdc42-dependent p38 MAPK pathway and a RhoA- and Cdc42-independent ERK1/2 pathway, thereby activating PPAR_. Statins also activate PPAR_ via COX-2–dependent pathway. These effects of statins may explain their antiatherogenic actions.

Adam g. Goodwill ET al[103]. beginning at seven weeks of age, male OZR was treated with gemfi brozil, probucol, atorvastatin, or simvastatin (in chow) for 10 weeks. Subsequently, plasma and vascular samples were collected for biochemical/molecular analyses, while arteriolar reactivity and microvessel network structure were assessed by using established methodologies after 3,6, and 10 weeks of drugs therapy. While the positive impact of chronic statin treatment on vascular outcomes in the metabolic syndrome are independent of changes to total cholesterol, and are more strongly associated with improvements to vascular NO bioavailability and attenuated inflammation, these results provide both a spatial and temporal framework for targeted investigation into mechanistic determinant of vasculopathy in the metabolic syndrome.

Goldstein ET al[104]. Laboratory experiments suggest statin reduce stroke severity and improve outcomes. The Stroke prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was a placebo-controlled, randomized trial designed to determine whether treatment with atorvastatin reduces strokes in subjects with recent stroke or transient ischemic attack (n≤4731). We analysed SPARCL trial data to determine whether treatment favourably shifts the distribution of severities of ischemic. The present explanatory analysis suggests that the outcomes of recurrent ischemic cerebrovascular events might be improved among statin users as compared with nonusers.

Takafumi H, ET al[105]. The JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study was a prospective, randomized, open-label, parallel group study with blind end point evaluation conducted at 33 centers in Japan. A total of 307 patients with ACS undergoing IVUS-guided percutaneous coronary intervention were randomized, and 252 patients had evaluable IVUS examinations at baseline and 8 to 12 months' follow-up. Patients were randomly assigned to receive either 4 mg/day of pitavastatin or 20 mg/day of atorvastatin. The primary end point was the percentage change in nonculprit coronary PV. The mean percentage change in PV was _16.9 _ 13.9% and _18.1 _ 14.2% (p _ 0.5) in the pitavastatin and atorvastatin groups, respectively, which was associated with negative vessel remodeling. The upper limit of 95% confidence interval of the mean difference in percentage change in PV between the 2 groups (1.11%, 95%

confidence interval: _2.27 to 4.48) did not exceed the pre-defined noninferiority margin of 5%.

Thomasine; T.Mazzoneet al[106]. This *post hoc*analysis compared the effects of treatment with Ezetimibe/simvastatin 10/20 mg vs. atorvastatin 10 and 20 mg/day and Ezetimibe/simvastatin 10/40 mg/day vs. atorvastatin 40 mg/day on the cholesterol content of lipoprotein subclasses in the modified intent-to-treat (mITT) population (n≤1013) and in subgroups of patients with triglyceride (TG) levels <200 mg/dl (n≤200 mg/dl (2.6 mmol/l) (n≤413). Results: Ezetimibe/simvastatin significantly reduced low-density lipoprotein cholesterol (LDL-C) subclasses LDL_1-c, LDL_2-C and LDL_3-C; real LDL-C (LDL-C); intermediate-density lipoprotein cholesterol (IDL-C) IDL_1-C,IDL_2-C; very low-density lipoprotein cholesterol (VLDL-C), $VLDL_3$-C; and remnant-like lipoprotein cholesterol (RLP-C) from baseline more than atorvastatin at all dose comparisons ($p<0.01$) in the mITT population. Significant improvements were also observed in high-density lipoprotein cholesterol (HDL-C) subclass HDL_3-C at the Ezetimibe/simvastatin 10/20 mg vs. atorvastatin 20 mg and highest dose comparisons ($p<0.001$) and in $VLDL_{1+2}$-C at the lowest and highest dose comparisons ($p<0.0001$). changes in LDL_4-C and LDL-C

Ole Faergeman ET al[107]. The trials compared atorvastatin 80 mg/day with moderate-dose statin therapy (simvastatin 20 to 40 mg/day in IDEAL and atorvastatin 10 mg/day in TNT) in patients with clinically evident coronary heart disease or a history of myocardial infraction. The outcome measurement in the present research was CVE occurring after the first year of the trial. After adjusting for age, gender, and study, risk of CVEs increased with increasing TGs ($p<0.001$ for trend across quintiles of TGs). Patients in the highest quintile had a 63% higher rate of CVEs than patients in the lowest Quintile (hazard ration 1.63, 95% confidence interval 1.46 to 1.81) and the relation of TGs to risk was apparent even within the normal range of TGS. Even slightly increased TG levels are associated with higher risk of recurrence of CVEs in statin-treated patients and should be considered a useful marker of risk.

Akiko Tsujimoto et al[108]. We examined effects of a physiologic concentration of pitavastatin (0.01 mmol/L) on oxidant-induced apoptosis in cultured human vascular smooth muscle cells (VSMCs). Apoptosis was induced in VSMCs by hydrogen

peroxide (H2O2, 300 mmol/L), as evidenced by in situ nick end-labeling and scanning electron microscopy. This apoptotic response was accompanied by increased activation of mitogen-activated protein kinases (MAPKs—ie, increases in the phosphorylated forms of extracellular signal-regulated kinase (p-ERK), c-Jun N-terminal kinase (p-JNK), and p38 MAPK (p-p38 MAPK). Although pitavastatin alone did not induce VSMC death, pretreatment with pitavastatin significantly enhanced H2O2- induced apoptosis and prolonged activation of JNK and p38 MAPK (for up to 24 h) but not ERK. Expression of MAPK phosphatase-1 (MKP-1) also was upregulated by H2O2, but this was not affected by pitavastatin. The apoptosis accelerating effect was observed also in simvastatin but not in pravastatin. Treating VSMCs with mevalonate, farnesyl pyrophosphate, or geranylgeranyl pyrophosphate completely blocked the statin-induced enhancement of VSMC apoptosis, suggesting that protein prenylation is critically involved. It thus appears that pitavastatin enhances H2O2-induced VSMC apoptosis, at least in part, via increases in MAPK activation and protein prenylation, but independently of MKP-1 expression, which consequently results in reduction of VSMC population.

Hitoshi Ando, ET al[109]. Aims**:** To compare the effects of grapefruit juice (GFJ) on the pharmacokinetics of Pitavastatin and atorvastatin. Methods**:** In a randomized, four-phase crossover study, eight healthy subjects consumed either GFJ or water t.i.d. for 4 days in each trial. On each final day, a single dose of 4 mg pitavastatin or 20 mg atorvastatin was administered. Results GFJ increased the mean AUC 0 -24 of atorvastatin acid by 83% (95% CI 23–144%) and that of pitavastatin acid by 13% (-3 to 29%).Conclusions: Pitavastatin, unlike atorvastatin, appears to be scarcely affected by the CYP3A4-mediated metabolism.

Kouji Kajinami, et al[110]. The use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, statins, has been shown to reduce major cardiovascular events in both primary and secondary prevention, and statins became one of the most widely prescribed classes of drugs throughout the world. Previously, statins have been well tolerated and have shown favorable safety profiles. However, the voluntary withdrawal of cerivastatin from the market because of a disproportionate number of reports of rhabdomyolysis-associated deaths drew attention to the pharmacokinetic profile of statins, which may possibly have been

related to serious drug-drug interactions. Pitavastatin (NK-104, previously called itavastatin or nisvastatin, Kowa Company Ltd., Tokyo) is a novel, fully synthetic statin, which has a potent cholesterol-lowering action. The short-term and long-term lipid-modifying effects of pitavastatin have already been investigated in subjects with primary hypercholesterolemia, heterozygous familial hypercholesterolemia, hypertriglyceridemia, and type-2 diabetes mellitus accompanied by hyperlipidemia. Within the range of daily doses from 1 to 4 mg, the efficacy of Pitavastatin as a lipid-lowering drug seems to be similar, or potentially superior, to that of atorvastatin. According to the results of pharmacokinetic studies, pitavastatin showed favorable and promising safety profile; it was only slightly metabolized by the cytochrome P450 (CYP) system, its lactone form had no inhibitory effects on the CYP3A4-mediated metabolism of concomitantly administered drugs; P-glycoprotein-mediated transport did not play a major role in its disposition, and pitavastatin did not inhibit P-glycoprotein activity.

Tomoya Mita1, E Tal[111]. Aims/Introduction: The distinct effects of different statins on glycemic control have not been fully evaluated. In this open-label, prospective, cross-over clinical trial, we compared the effects of pitavastatin and atorvastatin on glycemic control in type 2 diabetic patients with hypercholesterolemia. Materials and Methods: A total of 28 Japanese type 2 diabetics with hypercholesterolemia treated with rosuvastatin (2.5 mg/day) for at least 8 weeks were recruited to this quasi-randomized cross-over study. At study entry, the patients assigned to sequence 1 received pitavastatin (2 mg/day) for 12 weeks in period 1 and atorvastatin (10 mg/day) for another 12 weeks in period 2, whereas patients assigned to sequence 2 received atorvastatin (10 mg/day) for 12 weeks in period 1 and pitavastatin (2 mg/day) for another 12 weeks in period 2. Blood samples were collected at three visits (baseline, after 12 and 24 weeks). Results: Lipid control was similar in both statins. The difference in glycated hemoglobin between pitavastatin and atorvastatin treatments was _0.18 (95% confidence interval _0.34 to _0.02; P = 0.03). Compared with atorvastatin, pitavastatin treatment significantly lowered the levels of glycoalbumin, fasting glucose and homeostasis model assessment of insulin resistance. Conclusions: Our results showed that treatment with pitavastatin had a more favorable outcome on glycemic control in patients with type 2 diabetes compared with atorvastatin.

Ping-Yen Liu, ET al[112]. Evidence about the efficacy and safety of statin treatment in high-risk patients with hypercholesterolemia is available for some populations, but not for ethnic Chinese. To test the hypothesis that treatment with pitavastatin (2 mg/day) is not inferior to treatment with atorvastatin (10 mg/day) for reducing lowdensity lipoprotein cholesterol (LDL-C), a 12-week multicenter collaborative randomized parallel-group comparative study of high-risk ethnic Chinese patients with hypercholesterolemia was conducted in Taiwan. In addition, the effects on other lipid parameters, inflammatory markers, insulin-resistance-associated biomarkers and safety were evaluated. *Methods and Results:* Between July 2011 and April 2012, 251 patients were screened, 225 (mean age: 58.7 ± 8.6; women 38.2% [86/225]) were randomized and treated with pitavastatin (n = 112) or atorvastatin (n = 113) for 12 weeks. Baseline characteristics in both groups were similar, but after 12 weeks of treatment, LDL-C levels were significantly lower: pitavastatin group = −35.0 14.1% and atorvastatin group = −38.4 ± 12.8% (both: $p < 0.001$). For the subgroup with diabetes mellitus (DM) (n = 125), LDL-C levels (−37.1 ± 12.9% vs. −38.0 ± 13.1%, $p = 0.62$) were similarly lowered after either pitavastatin (n = 63) or atorvastatin (n = 62) treatment. Triglycerides, non-high density lipoprotein cholesterol, and apoprotein B were similarly and significantly lower in both treatment groups. In non-lipid profiles, HOMA-IR and insulin levels were higher to a similar degree in both statin groups. Hemoglobin A1C was significantly ($p = 0.001$) higher in the atorvastatin group but not in the pitavastatin group. Both statins were well tolerated, and both groups had a similar low incidence of treatment-emergent adverse events. *Conclusion:* Both pitavastatin (2 mg/day) and atorvastatin (10 mg/day) were well tolerated, lowered LDL-C, and improved the lipid profile to a comparable degree in high-risk Taiwanese patients with hypercholesterolemia.

R.C. Maranhaol ET al[117]. We studied 56 CAD patients (56p5 yo) confirmed by cineangiocoronariography; 28 patients were being treated with 20 mg/day simvastatin and 28 were not treated. An artificial nanoemulsion (LDE) was used as lipid donor to HDL LDE labelled with 3H-TG and 14C-FC or 3H-CE and 14C-PL was incubates with plasma samples for 1h. After chemical precipitation, the supernatant containing

HDL was counted for radioactivity; HDL size was measured by laser-light-scattering. Our results show that simvastatin is able to modify the lipid flux to HDL, which may change the composition and metabolism of the lipoprotein. The diminished ability to received lipids, which is consistent with diminished CETP action elicited by statin use, may increase the stability of the lipoprotein particles.

Valentine Charlton-Menys et al[119]. Type 2 diabetes patients randomly allocated to 10 mg/day atorvastatin (n≤1154) or to placebo (n≤1196)for 1 year were studied to compare spontaneous and statin-induced apolipoprotein B (apo B) concentrations (a measure of LDL particle concentration) at LDLC and non-HDL cholesterol (non-HDLC) concentrations proposed as statin targets in type 2 diabetes. Results: Patients treated with atorvastatin produced lower serum apo B concentration at any given LDLC concentration than patients on placebo. An LDLC concentration of 1.8 mmol (70 mg/dL) during atorvastatin treatment was equivalent to a non-HDLC concentration of 2.59 mmol/dL (100 mg/dL) or an apo B concentration of 0.8g/L. At the more conservative LDLC targets of 2.59mmol/L (100 mg/dL. At the more conservation LDLC target of 2.59 mmol/L (100 mg/dL) and 3.37 mmol/L (130mg/dL) for non-HDLC, however, the apo B concentration exceeded the 0.9-g/L value anticipated in the recent Consequence Statements from the American Diabetes Association and the American College of Cardiology. The apo B concentration provides a more consistent goal for statin treatment than the LDLC or non-HDLC concentration.

William Insull et al[121]. A Randomized (3:2), Open-label, Blinded Endpoint (PROBE) study. Methods following ≤4 weeks without lipid-modifying therapies, 193 patients with dyslipidemia were treated with NER/S(n≤114; 1000/40 mg/day, weeks 1 to 4; 2000/40 mg/day weeks 5 to 12) or atorvastatin (n≤79; 40 mg/day, weeks 1 to 12). Compared to atorvastatin, NER/S had a larger beneficial effect on HDL-C(primary end point: 30.1 ±2.3% and 9.4± 2.6% respectively; P<.001), and similar effects on LDL-C and non HDL-C. Two thirds of patients, treated with NER/S concurrently attained LDL-C (CV risk-adjusted goals), HDL-C (≤40 mg/dl), and TG (<150mg/dl) targets, compared to one-third of patients treated with atorvastatin (P<.001). Flushing was the most common treatment-emergent adverse event (TEAE) (67.5% NER/S and 10.1 % atorvastatin; P<.001. Seventy-five per cent of flushing

episodes were mild to moderate. More patients treated with NER/S and 10.1% atorvastatin; P<.001); the most common TEAE was flushing. Compared to atorvastatin, NER/S provided superior improvements in HDL-C and LDL-C. Treatment with NER/S should be considered for patient with dyslipidemia requiring comprehensive lipid control.

Patricia Tung et al[122]. The Previous studies have shown seasonal variation in lipids. To understand whether this variation exists in patient with acute coronary syndrome \s receiving statins, we examined data from the PROVE IT- TIMI 22 study. At baseline, no significant difference in low density lipoprotein (LDL) cholesterol was observed when stratified by season. However, a statistically significant difference in high-density lipoprotein cholesterol between winter (37 mg/dl) and summer (39 mg/dl) was observed ($p<0.001$) at baseline. On treatment, median LDL cholesterol was 102 mg/dl in winter versus 96 mg/dl in summer ($p<0.001$) for the pravastatin group and 68 mg/dl in winter versus 62 mg/dl in summer ($p<0.001$) for the atorvastatin group. Median high-density lipoprotein cholesterol was 43 mg/dl in summer versus 39 mg/dl in winter in the atorvastatin group ($p<0.001$). More patentsachieved LDL cholesterol <100 mg/dl in summer at 56% versus 47% in winter in the pravastatin group ($p\leq0.11$). Achievement of LDL cholesterol <70mg/dl was also higher in summer than winter. In conclusion, this was the first evidence of seasonal variability in cholesterol in patient with acute coronary syndromes treated with statins. This Variability affected achievements of National Cholesterol Education Program goals and may affect management decisions based on season of collection.

Peter H.Jones et al[123]. As prospectively planned, data were pooled from three randomized, double-blind, phase 3 studies of patients with low-density lipoprotein cholesterol (LDL-C) ≤130 mg/dL, triglycerides (TG)≤150 mg/dl. And high-density lipoprotein cholesterol (HDL-C) <40mg/dl (men) or <50 mg/dl (women). A total of 2715 patients were randomly assigned to 12-week treatment with fenofibric acid 135 mg monotherapy; Fenofibric acid + low-dose statin increased HDL-C (18.1% vs. 7.4%) and reduced LDL-C (-33.1% vs. -5.1%) versus low-dose statin monotherapy and reduced LDL-C (-33.1% vs.-5.1%)versus fenofibric acid monotherapy (p<.001

for all). Fenofibric acid+ moderate-dose statin increased HDL-C (17.5% vs. 8.7%) and reduced TG (-42.0% vs. -23.7%) versus moderate-dose statin monotherapy and reduced LDL-C (-34.6% vs. -5.1%) versus fenofibric acid monotherapy (P<0.001 for all). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapy. No rhabdomyolysis was reported.

CHAPTER V

AIM OF THE STUDY

5. AIM OF THE STUDY

The purposes of the study were:

a. To assess the percentage reduction in lipid levels achieved in pitavastatin and atorvastatin. Using optimal guideline based prophylactic treatment of dyslipidemia.
b. To find the co-relation between the pitavastatin and atorvastatin administered and changes of lipid levels
c. To define patient groups who are at high risk for dyslipidemia.
d. To analyse the percentage of adverse effect in pitavastatin and atorvastatin.

CHAPTER VI

NEED FOR THE STUDY

6. NEED FOR THE STUDY

Nowadays large numbers of patients are taking Pitavastatin and Atorvastatin. Studies are going on in various parts of the world for the efficacy and safety of Pitavastatin and Atorvastatin in Dyslipidemia patients. So I selected this topic to find out the safety, efficacy and quality of life for Dyslipidemia patients in our population who were taking Pitavastatin and Atorvastatin.

CHAPTER VII

METHODOLOGY

7. METHODOLGY

This study was conducted in MEENAKSHI MISSION HOSPITAL AND RESEARCH CENTRE (MMHRC) in Madurai during July 2014-Feb 2015.

Study design: Randomized, Prospective and comparative study.

Sample size: 60 Patients

A total of 60 patients were included in the study in four groups of 15 patients in each group. Group-1 patients received Pitavastatin 1 mg tablet once in a day, Group-2 received Atorvastatin 20 mg tablet once in a day, Group-3 patients received Pitavastatin 2 mg tablet once in a day, and Group-4 received Atorvastatin 40 mg tablet once in a day For a period of 20 weeks. Pre index laboratory test values for the 5 month period before statin initiation were collected. Post index laboratory test values were captured after 9 weeks. At each follow visit, patient were assessed for lipid profile, adverse effect was asked. The patients were reviewed, and the lipid and safety profiles were repeated.

Patients measure the lipid level (LDL cholesterol, HDL cholesterol, Total cholesterol and triglycerides). Patients were asked to report their assessment of side effects during the study

The Pre index of Post index period was used to estimate the percentage change in lipid values for each laboratory value and to determine the efficacy, safety and quality of life in Dyslipidemia patient.

INCLUSIOIN CRITERIA

1. Patients aged ≥18 years with hypercholesterolemia and a history of CHD,
2. Clinical evidence of atherosclerosis or a CHD-risk equivalent (other clinical form of atherosclerotic disease [peripheral arterial disease, abdominal aortic

aneurysm or symptomatic carotid artery disease (transient ischemic attacks, stroke of carotid origin, or > 50% obstruction of a carotid artery)]

3. Baseline levels of LDL-C> 100mg/dl
4. HDL-C<40 mg/dl
5. Total cholesterol>200mg/dl
6. Triglycerides > 200 mg/dl and 500 mg/dl
7. Diabetes mellitus or ≥2 risk factors that confer a 10-year CHD-risk score>20% were eligible for randomization to the study.

EXCLUSION CRITERIA

1. A history of hypersensitivity to statins
2. Pregnancy/lactation
3. Active liver diseases/hepatic dysfunction
4. Patient having history of sever myalgia or myositis.
5. Serious or unstable medical or psychological condition that could compromise the patient's safety or successful trial participation.

Statistical Tool

The information collected regarding all the selected causes were recorded in a Master Chart. Data analysis was done with the help of computer using Graph Pad In Stat DTCG (GPI v3.0)

Using this software frequencies, percentages, means, standard, deviations. Student unpaired t-test and 'p' values were calculated. Student unpaired t-test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A'p' value less than 0.05 is taken to denote significant relationship.

CHAPTER VIII

OBSERVATIONS OF RESULTS

8. OBSERVATION AND RESULTS

Clinical characteristics

In this study totally 100 patients were examined. 80 of them had CAD. Due to side effects and other reasons 20 patients discontinued from treatment.

Only 60 patients of them had regular treatment.

The baseline clinical characteristics of patients with Pitavastatin and Atorvastatin are summarized in the table. Out of the 60 patients in the study Diabetes was present in 20 (20%) and Hypertension in 32 (32%) at baseline.

These patients were significantly older, had a higher systolic BP and a higher incidence of Hypertension

Age Distribution

Although the age differed between the Pitavastatin and Atorvastatin group, the incidence of Dyslipidemia in patients older than 50 years were higher when compared with younger patients.

Statistical analysis using student unpaired t-test shows that the p-value is 0.3396 and 0.0773 since the p value is greater than 0.05 the incidence of Dyslipidemia in elderly patients is not statistically significant.

PROFILE OF CASES STUDIED

Table.1 Age Distribution

Age Group	Pitavastatin 1 mg		Atorvastatin 20 mg		Pitavastatin 2 mg		Atorvastatin 40mg	
	No.	%	No.	%	No.	%	No.	%
Up to 50 yrs	6	40	8	53.3	7	46.7	5	33.3
Above50 yrs	9	60	7	46.7	8	53.3	10	66.7
Total	15	100	15	100	15	100	15	100
Range	32-68 yrs.		34-66 yrs.		41-65 yrs.		34-77 yrs.	
Mean	54.3 yrs.		50.7 yrs.		51.7 yrs.		57.5 yrs.	
SD	10.5 yrs.		108 yrs.		6.0 yrs.		10.06 yrs.	
P Value	0.3396				0.0773			

Figure.1

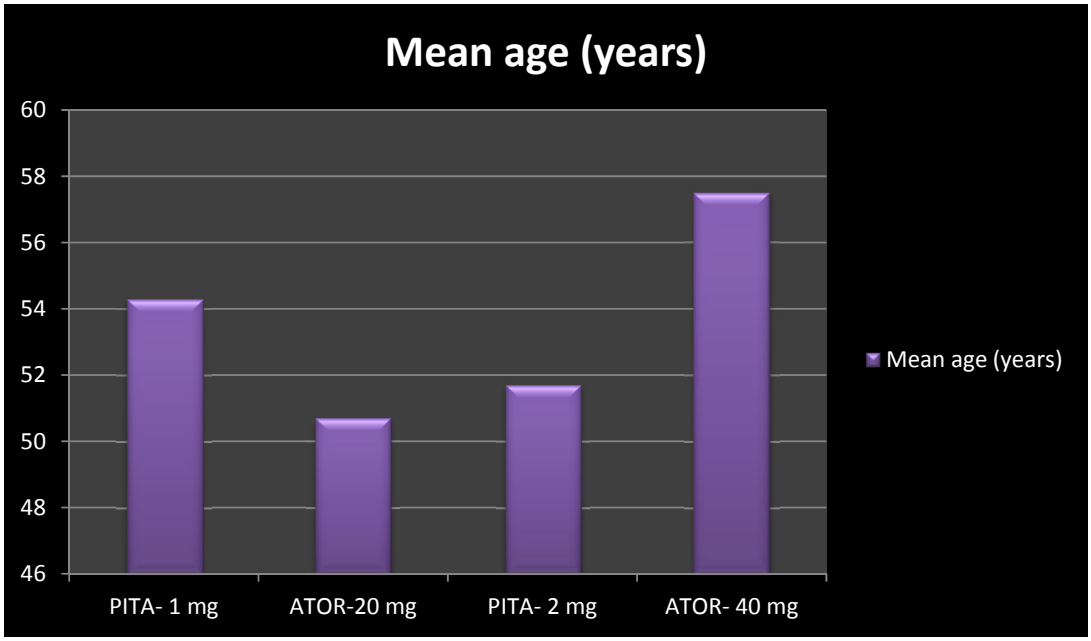


Table.2 Sex Distribution

Sex	Pitavastatin 1 mg		Atorvastatin 20 mg		Pitavastatin 2 mg		Atorvastatin 40 mg	
	No	%	No	%	No	%	No	%
Male	13	86.7	12	80	10	66.7	12	80
Female	2	13.3	3	20	5	33.33	3	20
Total	15	100	15	100	15	100	15	100
P value	0.5				0.3408			

The Sex differed between the Pitavastatin and Atorvastatin groups, the incidence of Dyslipidemia in patients Male were higher when compared with Female Patients.

Since the p Value is greater than 0.05 the incidence of Dyslipidemia in Male patients is not statistically significant.

Figure.2

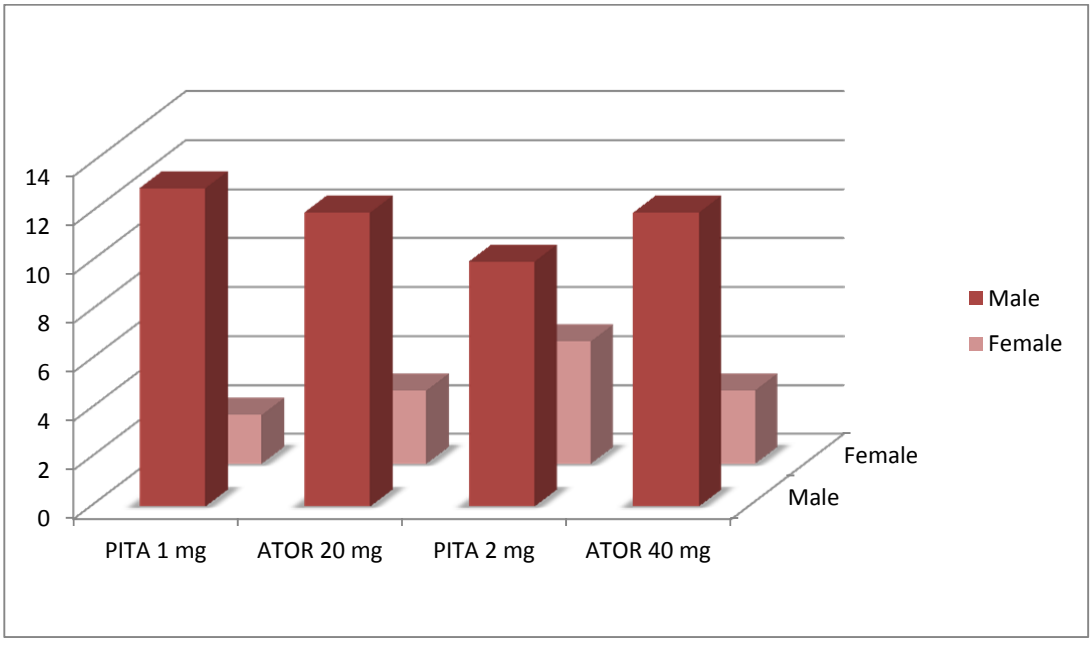
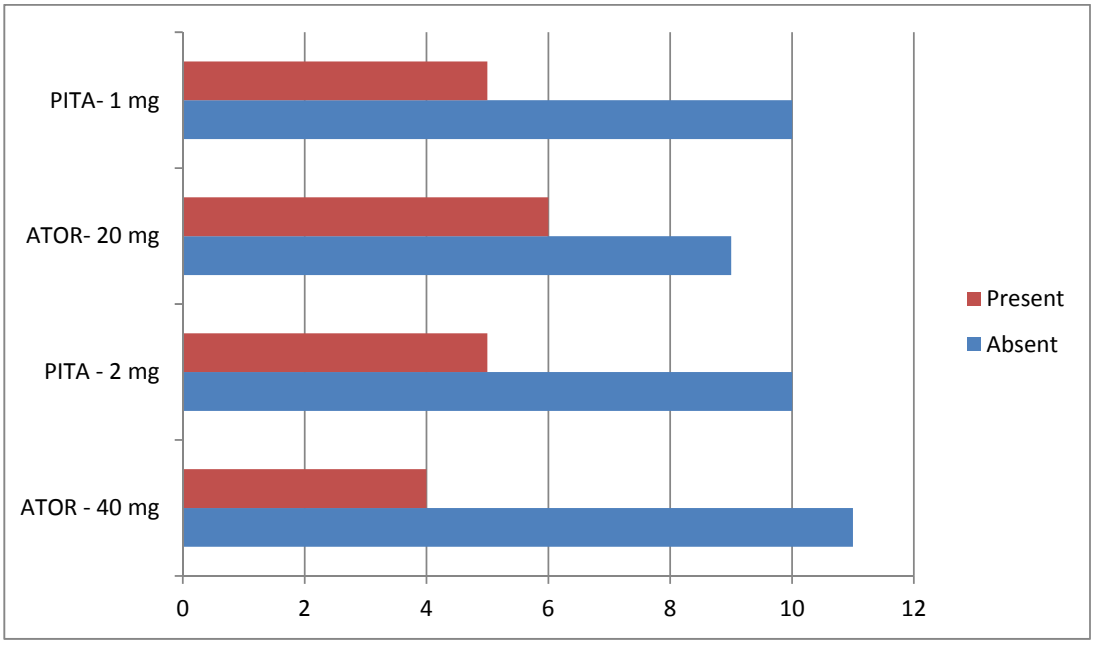


Table.3 Diabetes Mellitus

Diabetes Mellitus	Pitavastatin 1 mg		Atorvastatin 20 mg		Pitavastatin 2 mg		Atorvastatin 40 mg	
	No	%	No	%	No	%	No	%
Present	5	33.33	6	40	5	33.3	4	26.7
Absent	10	66.7	9	60	10	6.7	11	73.3
P Value	1.0				0.5			

The comparison of Dyslipidemia in Diabetic and Non diabetic patients did not show any significant difference. The graphical representation is shown in Figure.

Figure.3



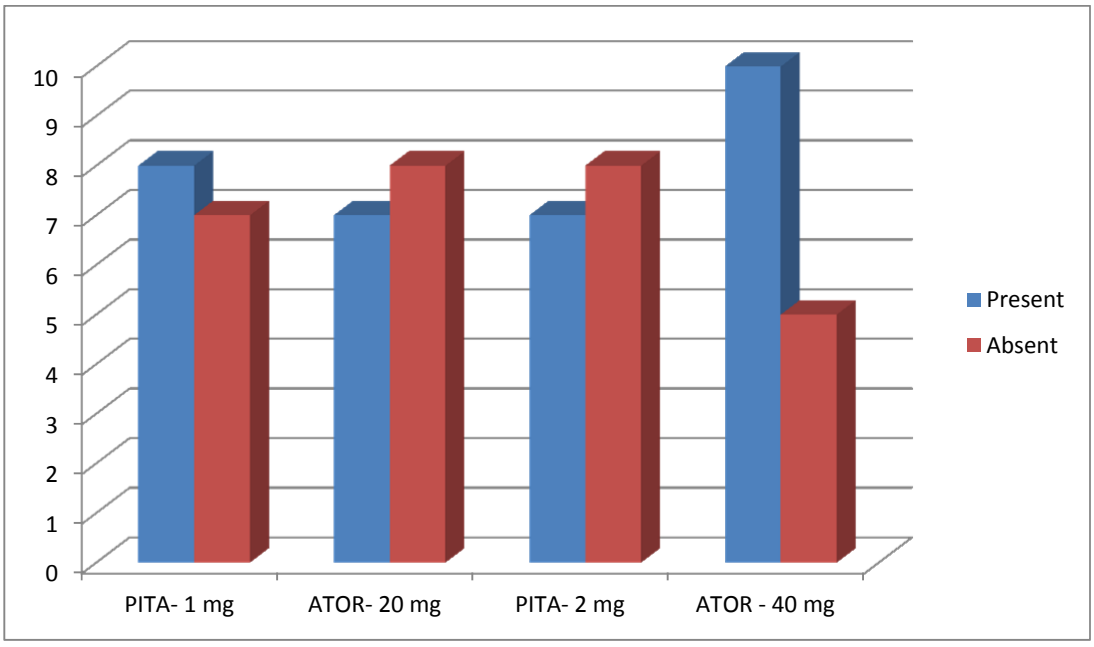
Statistical analysis using student unpaired t-test shows that the p value is 1.0 and 0.5. Since the p value is greater than 0.05, the Dyslipidemia in DM and Non DM patients is not statistically significant.

Table.4 Hypertension

Hypertension	Pitavastatin 1 mg		Atorvastatin 20 mg		Pitavastatin 2 mg		Atorvastatin 40 mg	
	No	%	No	%	No	%	No	%
Present	8	53.3	7	46.7	7	46.7	10	66.7
Absent	7	46.7	8	53.3	8	53.3	5	33.3
P Value	1.0				0.4612			

The comparison of Dyslipidemia in Hypertensive and Non Hypertensive patients did not show any significant difference. The graphical representation is show in Figure.4

Figure.4



Statistical analysis using student unpaired t-test shows that the p value is 1.0 and 0.4612. Since the p value is greater than 0.05, the Dyslipidemia in Hypertensive and Non Hypertensive patients is not statistically significant.

Table.5 Family History

Family History	Pitavastatin 1 mg		Atorvastatin 20 mg		Pitavastatin 2 mg		Atorvastatin 40 mg	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Present	-	-	2	13.3	1	6.7	1	6.7
Absent	15	100	13	86.7	14	93.3	14	93.3
P value	0.2414				1.0			

There is no significant difference in the Dyslipidemia in family history

Figure.5

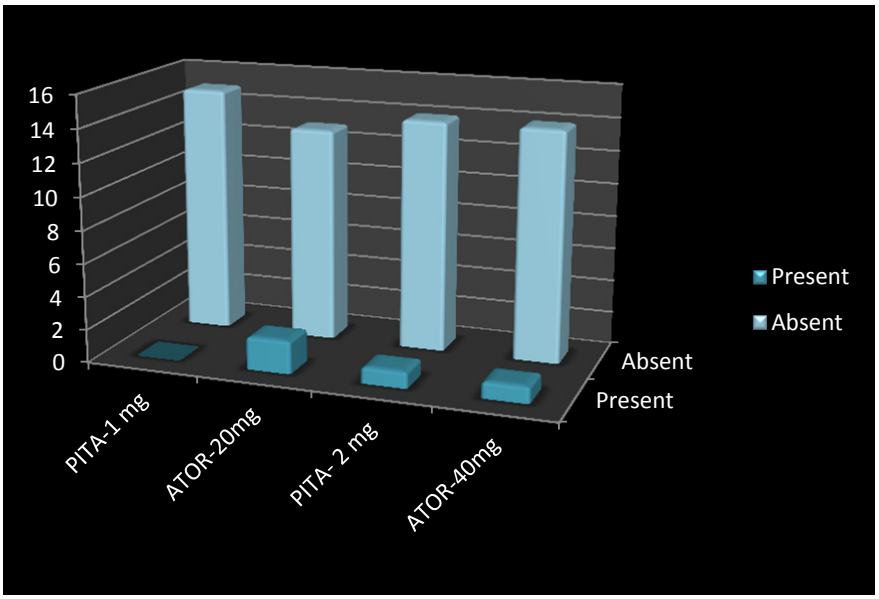
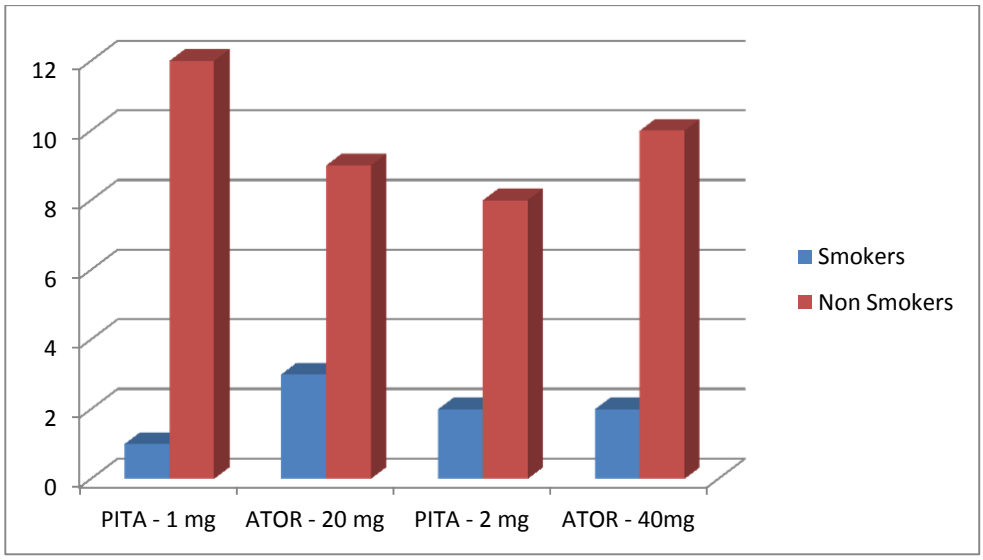


Table.6 Smoking (among males)

Smoking(among males)	Pitavastatin 1 mg (13)		Atorvastatin 20mg (12)		Pitavastatin 2 mg (10)		Atorvastatin 40mg (12)	
	No	%	No	%	No	%	No	%
Current smokers	-	-	-	-	1	10	1	8.3
Ex.Smokers	1	7.7	3	25	1	10	1	8.3
Total smokers	1	7.7	3	25	2	20	2	16.6
Non smokers	12	92.3	9	75	8	80	10	83
P values	0.2652				0.6316			

Figure.6



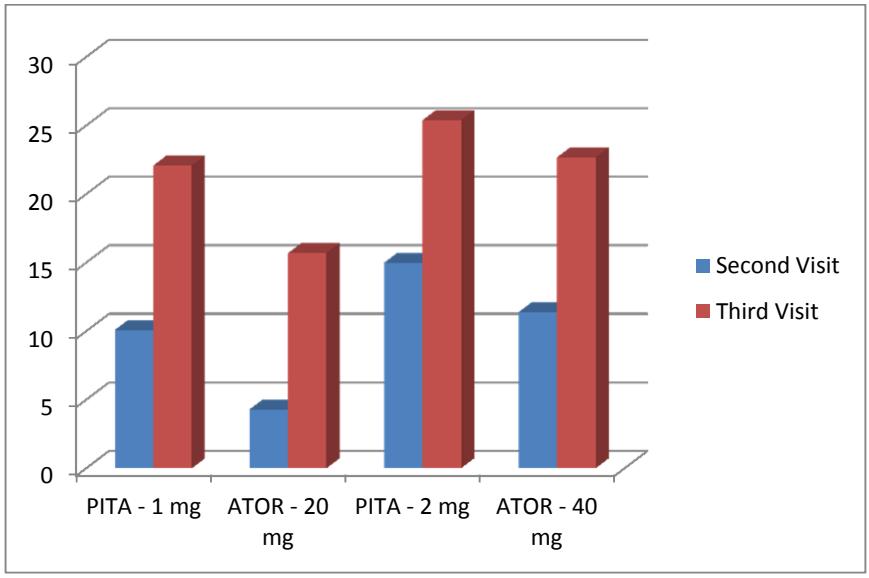
COMPARATIVE EFFICACY

Table.7 Changes in Total Cholesterol

Total cholesterol values at	**Pitavastatin 1 mg**	**Atorvastatin 20 mg**	**P value**	**Pitavastatin 2 mg**	**Atorvastatin 40 mg**	**P value**
First Visit	210.3±16	216.9±18.1	0.1495	243.4±47.1	234.9±34.1	0.6184
Second Visit	189.1±3.6	206.7±2.6	0.0354	217.7±4.2	206.3±6.5	0.0231
Third Visit	165.4±27.1	182.5±7.9	0.0318	172.4±4.7	180.6±4.1	0.0432
Changes during						
Second visit	21.1±18.4	10.1±7.5	0.0195	35.7±4.2	28.5±3.3	0.0177
Third visit	46.6±22.7	34.4±7.3	0.0472	68.9±6.2	58.1±7.9	0.0256
% of changes during						
Second Visit	10.1±4.0	4.3±3.2	0.00214	15.0±2.9	11.4±2.5	0.0457
Third Visit	22.1±2.7	15.7±3.9	0.047	25.4±4.2	22.7±3.7	0.0277

The comparison of total cholesterol in Pitavastatin and Atorvastatin patients were found to be statistically significant. The graphical representation is shown in Figure.7

Figure.7



It shows that Pitavastatin 1 mg is better than Atorvastatin 20 mg in the reduction of total cholesterol and also shows that Pitavastatin 2 mg is better than Atorvastatin 40 mg in the reduction of total cholesterol.

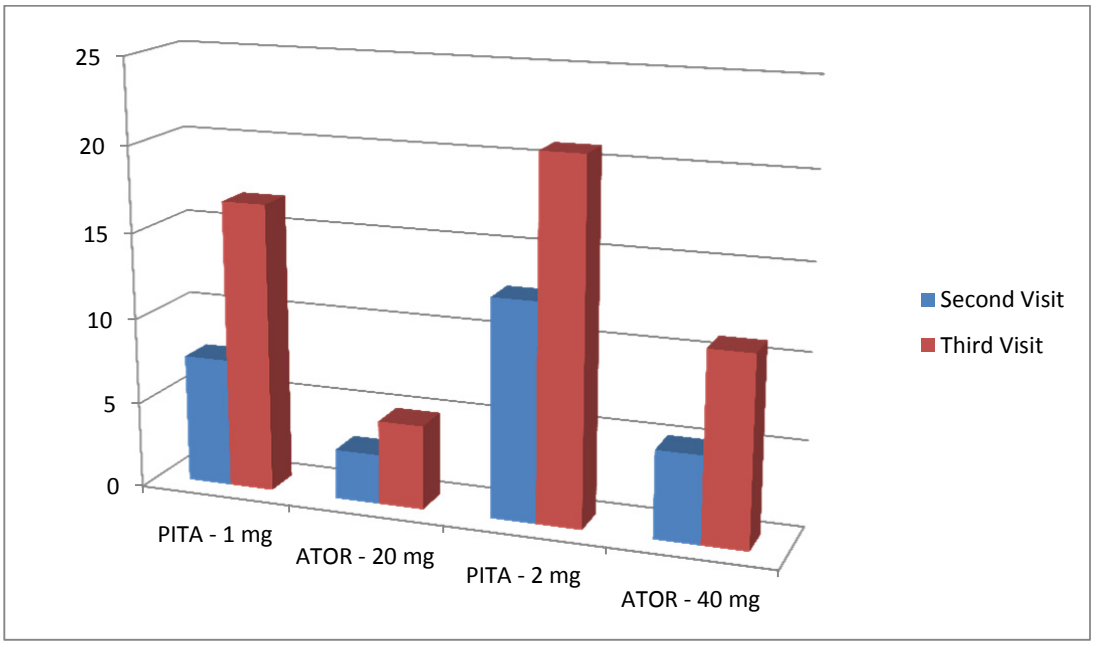
Statistical analysis using student unpaired t-test shows that the p value is less than 0.05; the total cholesterol in patient between Pitavastatin and Atorvastatin are found to be statistically significant.

Table.8 Changes in HDL

HDL Values at	Pitavastatin 1 mg	Atorvastatin 20 mg	P value	Pitavastatin 2 mg	Atorvastatin 40 mg	P value
First Visit	40.7±4.7	40.7±4.8	0.9523	41.9±4.9	41.5±4.9	0.6466
Second Visit	43.5±3.7	42±6.8	0.1172	46.5±2.4	43.5±3.5	0.0489
Third Visit	46.9±4.2	42.3±.6	0.0056	49.3±4.2	45.4±4.2	0.0305
Changes during						
Second visit	2.8±2.5	1.3±2.8	0.0227	5.6±1.6	2±2.4	0.0209
Third visit	6.5±2.6	1.6±5.1	0.0006	8.6±2.8	4.5±2.2	0.0465
% of changes during						
Second Visit	7.5±7.8	2.9±5.9	0.0378	12.7±4.6	5.1±5.9	0.0033
Third Visit	16.81±8.6	4.9±11.8	0.0015	20.9±8.8	11.0±13.2	0.047

The Comparison of HDL in Pitavastatin and Atorvastatin patients was found to be statistically significant. The graphical representation is shown in Figure.8

Figure.8



It shows that Pitavastatin 1 mg is better than Atorvastatin 20 mg increase of HDL and also shows that Pitavastatin 2 mg is better than Atorvastatin 40 mg increase of HDL.

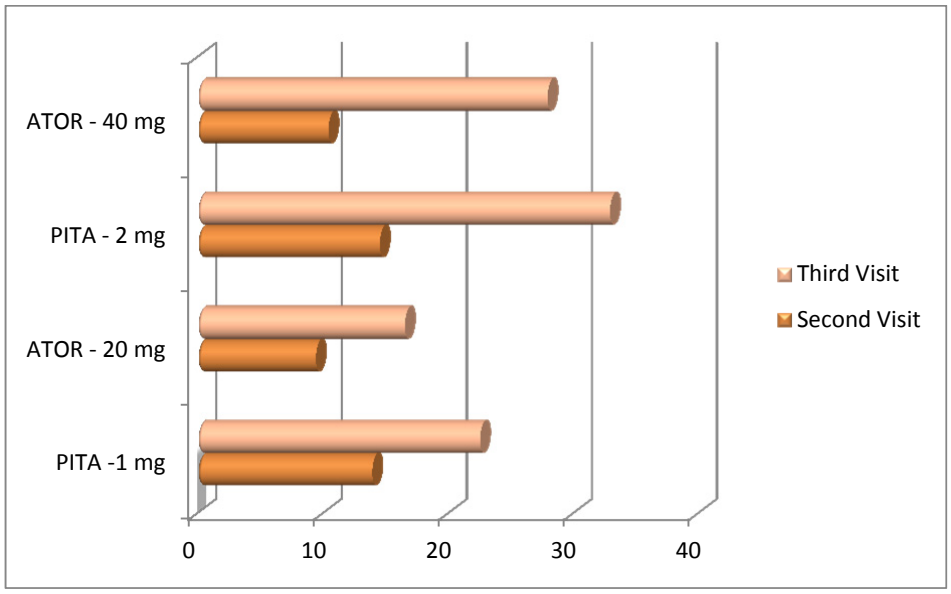
Statistical analysis using student unpaired t-test shows that the p value is less than 0.05; the total cholesterol in patient between Pitavastatin and Atorvastatin are found to be statistically significant.

Table.9 Changes in LDL

HDL Values at	Pitavastatin 1 mg	Atorvastatin 20 mg	P value	Pitavastatin 2 mg	Atorvastatin 40 mg	P value
First Visit	117.7±18.1	127±22.2	0.2365	150.7±36.4	141.8±43.8	0.2538
Second Visit	101.3±4.3	115.1±5.7	0.0392	128.9±2.3	122.7±1.9	0.0011
Third Visit	95.3±2.7	110.4±5.9	0.029	100.7±20.4	105.9±1.4	0.0082
Changes during						
Second visit	16.3±4.7	12.7±2.3	0.0355	21.8±2.5	19.1±1.9	0.039
Third visit	25.7±6.4	17.4±3.5	0.0027	50.9±4.7	36.5±6.5	0.0276
% of changes during						
Second Visit	14.0±2.4	9.5±4.7	0.0404	14.6±4.2	10.5±3.1	0.0428
Third Visit	22.6±3.3	16.6±4.1	0.0259	33±5.4	28±2.7	0.0277

The comparison of LDL in Pitavastatin and Atorvastatin patients was found to be statistically significant. The graphical representation is shown in Figure.9

Figure.9



It shows that Pitavastatin 1 mg is better than Atorvastatin 20 mg in the reduction of LDL and also shows that Pitavastatin 2 mg is better than Atorvastatin 40 mg in the reduction of LDL.

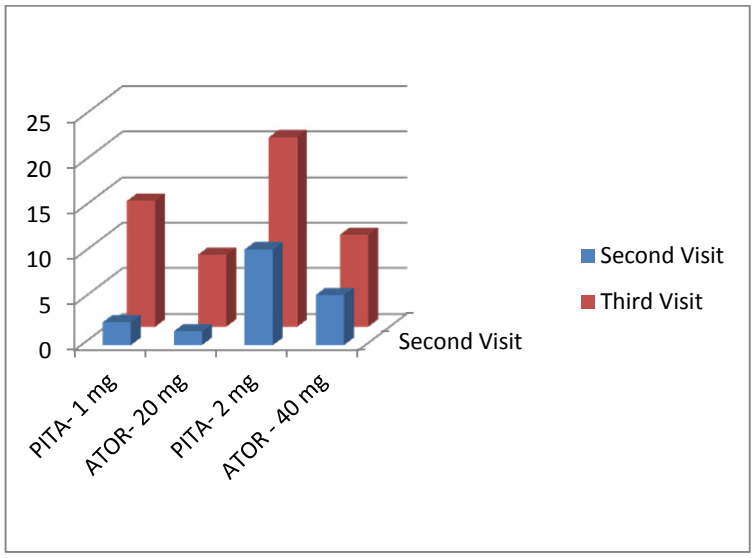
Statistical analysis using student unpaired t-test shows that the p value is less than 0.05; the total cholesterol in patient between Pitavastatin and Atorvastatin are found to be statistically significant.

Table.10 Changes in TGL

TGL Values at	Pitavastatin 1 mg	Atorvastatin 20 mg	P value	Pitavastatin 2 mg	Atorvastatin 40 mg	P value
First Visit	19.2.7±38.1	191.9±32	0.8519	181.5±29.9	187.3±31.3	0.6935
Second Visit	183.1±23.9	184.9±26.7	0.8357	165±21.6	176.9±23	0.8846
Third Visit	172.1±6.2	187.1±7.4	0.0331	151.8±3.5	169.5±4.7	0.0438
Changes during						
Second visit	9.6±2.6	7.0±2.4	0.0485	16.5±6.3	11.3±7.2	0.0418
Third visit	20.3±4.0	4.8±5.7	0.0001	28.8±6.2	23.9±2.8	0.0277
% of changes during						
Second Visit	2.5±13.4	1.5±21.6	0.3952	10.5±2.3	5.5±3.4	0.0319
Third Visit	13.8±13.9	7.9±43.4	0.0318	20.8±4.0	10.1±6.3	0.0066

The comparison of LDL in Pitavastatin and Atorvastatin patients was found to be statistically significant. The graphical representation is shown in Figure.10

Figure.11



It shows that Pitavastatin 1 mg is better than Atorvastatin 20 mg in the reduction of Triglycerides and also shows that Pitavastatin 2 mg is better than Atorvastatin 40 mg in the reduction of Triglycerides.

Statistical analysis using student unpaired t-test shows that the p value is less than 0.05; the total cholesterol in patient between Pitavastatin and Atorvastatin are found to be statistically significant.

Table.11 Changes in Systolic BP

Systolic BP at	Pitavastatin 1 mg	Atorvastatin 20mg	P value	Pitavastatin 2 mg	Atorvastatin 40mg	P value
First Visit	136.7±18.4	131.3±15.1	0.4341	133.3±17.2	143.3±13.5	0.1001
Second Visit	133.3±9.8	130.7±11.6	0.5036	131.3±10.6	135.3±8.3	0.3352
Third Visit	124.5±9.3	128±6.8	0.3664	131.7±5.8	131.5±6.9	1.0
Changes during						
Second visit	3.3±15.4	0.7±15.8	0.6362	2.0±15.2	8.0±9.4	0.099
Third visit	14.5±16.3	3.3±17.2	0.0968	3.3±16.7	13.1±11.1	0.1196
% of changes during						
Second Visit	1.2±12.312.9	0.4±	0.85	0.4±11.1	5.1±6.7	0.1494
Third Visit	9.3±12.3	1.3±	0.1503	1.1±12.1	8.6±7.1	0.1466

The comparison of systolic BP in Pitavastatin and Atorvastatin patients did not show any significant difference. The graphical representation is shown in Figure 11

Figure.11

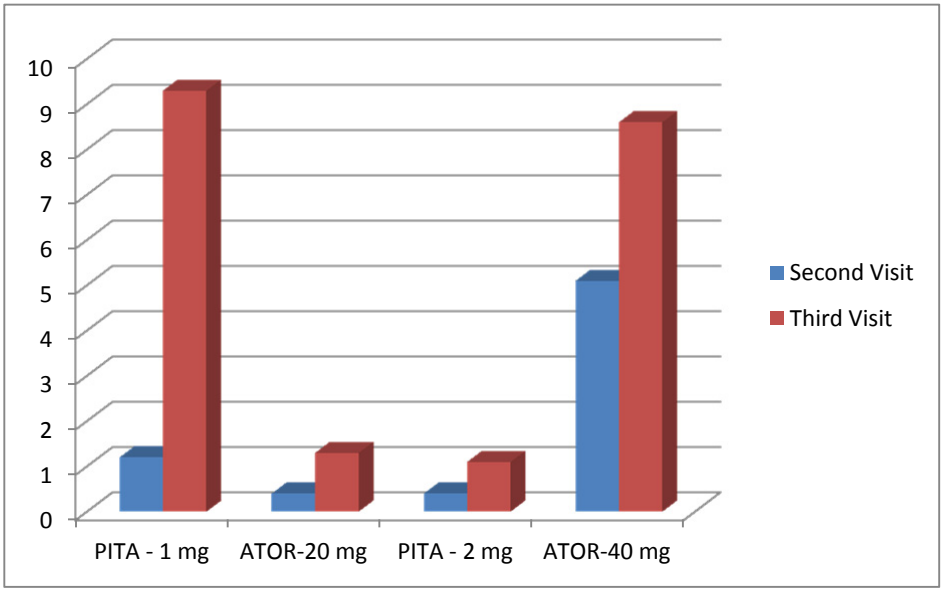
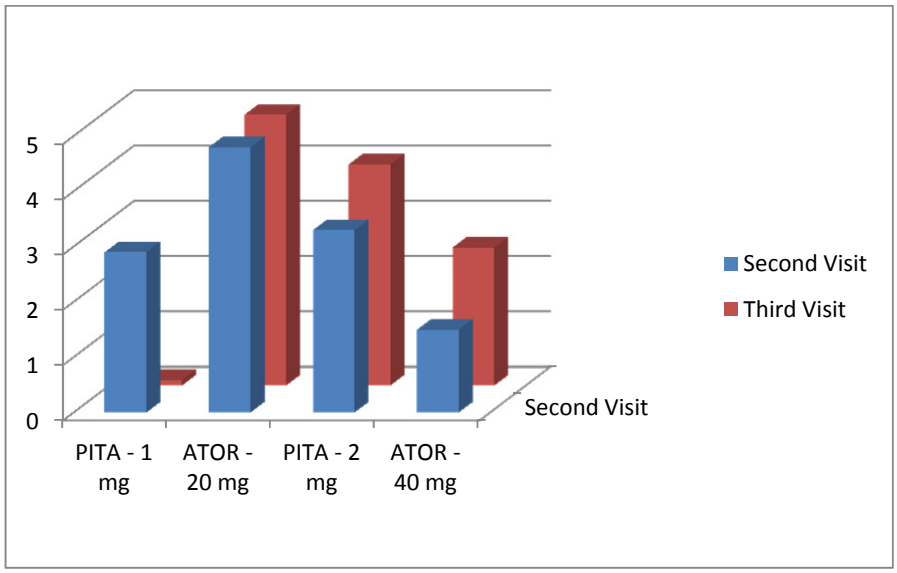


Table.12 Changes in Diastolic BP

Diastolic BP at	Pitavastatin 1 mg	Atorvastatin 20 mg	P value	Pitavastatin 2 mg	Atorvastatin 40 mg	P value
First Visit	76.7±8.2	76±9.1	0.7406	94.7±5.2	77.3±5.9	0.2184
Second Visit	78±6.8	78.7±7.4	0.9052	76.7±4.9	78.0±4.1	0.4169
Third Visit	76.4±5.0	78.9±5.2	0.2736	77.5±4.5	78.5±5.5	0.677
Changes during						
Second visit	1.3±11.3	2.7±16.6	0.6902	2.0±8.6	0.7±8	0.6269
Third visit	0.9±9.4	2.7±10.3	0.3541	2.5±8.7	1.5±8.0	0.6008
% of changes during						
Second Visit	2.9±14.7	4.8±14.7	0.5787	3.3±11.6	1.5±10.6	0.6919
Third Visit	0.1±13.7	4.9±14.4	0.319	4.0±11.7	2.5±11.0	0.6008

The comparison of Diastolic BP in Pitavastatin and Atorvastatin patients did not show any significant difference. The graphical representation is shown in Figure.12

Figure.12



RELATIONSHIP BETWEEN LIPID PROFILE AND AFTER VARIABLES

Table.13 Incidence of Side effects

Side Effects	Pitavastatin 1 mg		Atorvastatin 20 mg		Pitavastatin 2 mg		Atorvastatin 40 mg	
	No	%	No	%	No	%	No	%
Yes	1	6.7	2	13.3	1	6.7	2	13.3
No	14	93.3	13	86.7	14	93.3	13	86.7
P Value	0.5				0.5			

The Side effects differed between the Pitavastatin and Atorvastatin groups; the incidence of Side effects in Pitavastatin and Atorvastatin patients is not statistically significan

Figure.13

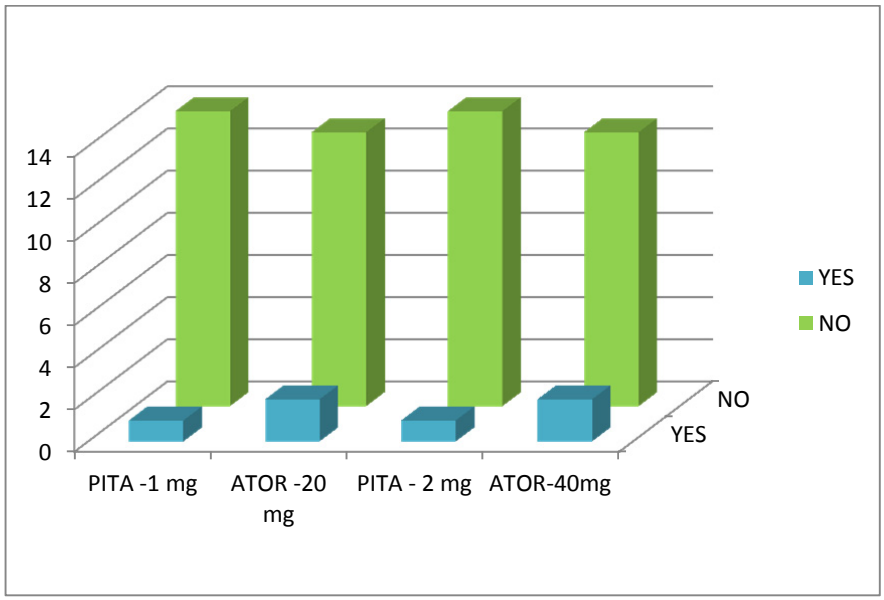
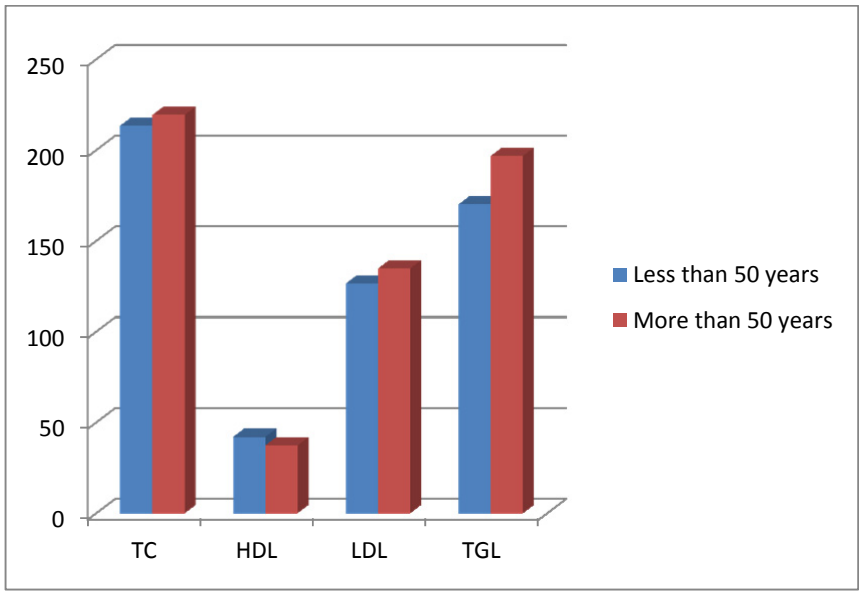


Table.14 Age and Lipid Profile

Lipid Profile								
Age group	**Total Cholesterol mg/dl**		**HDL mg/dl**		**LDL mg/dl**		**TGL mg/dl**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Less than 50	213.6	14.9	42.1	5.2	126.6	16.0	170.2	18.3
More than 50	219.5	19.4	37.4	3.8	134.9	12.1	196.9	13.3
P value	0.6679		0.1248		0.5997		0.6055	

The relationship between age and lipid profile patients was found to be statistically not significant the graphical representation is shown in fig14

Figure.14



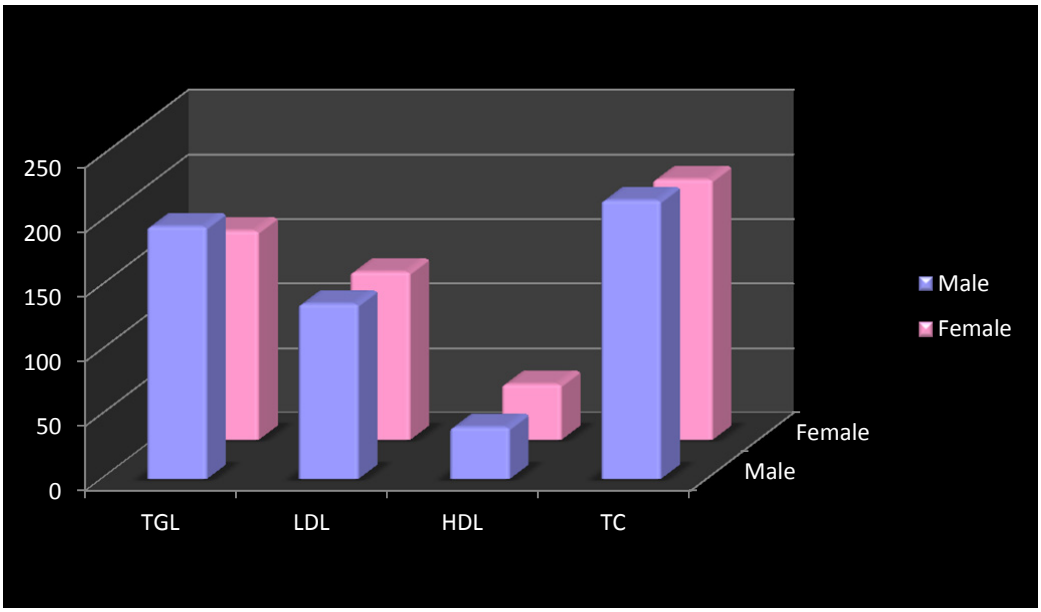
Statistical analysis using student unpaired t-test shows that the p value is greater than 0.05; the drug used in age and lipid profile patients were found to be statistically not significant

Table.15 Sex and Lipid Profile

Sex	Total Cholesterol mg/dl		HDL mg/dl		LDL mg/dl		TGL mg/dl	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Male	215.9	17.5	40.2	4.5	135.7	33.4	195.6	64.7
Female	201.8	9.3	43.2	5.0	13.02	35.1	162.0	61.2
P Value	0.0795		0.1042		0.6152		0.1411	

The relationship between Sex and lipid profile patients was found to be statistically not significant the graphical representation is shown in figure.15

Figure.15



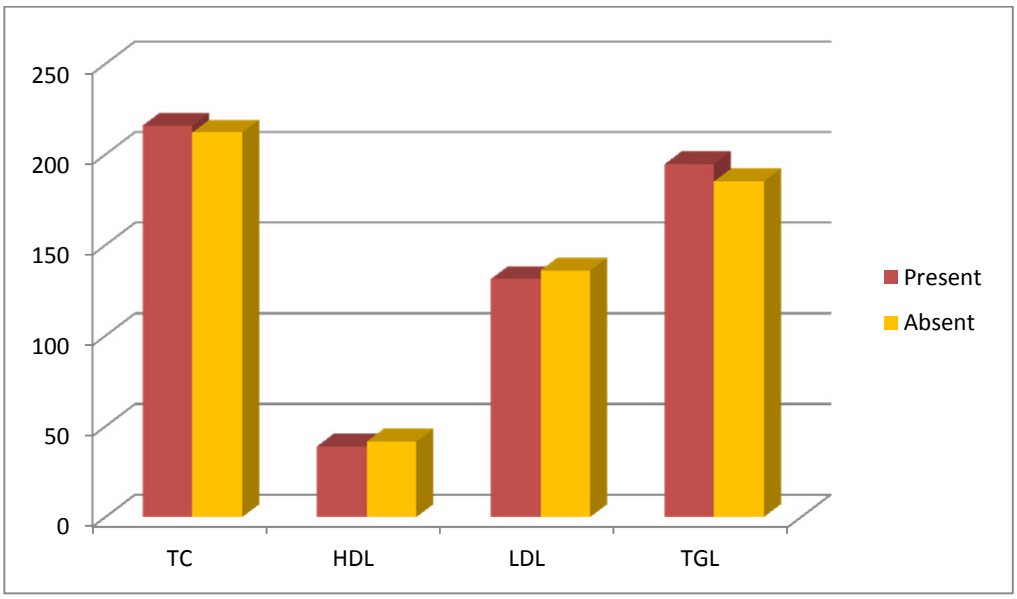
Statistical analysis using student unpaired t-test shows that the p value is greater than 0.05; the drug used in sex and lipid profile patients were found to be statistically not significant.

Table.16 Diabetes Mellitus and Lipid profile

DM	Total Cholesterol mg/dl		HDL mg/dl		LDL mg/dl		TGL mg/dl	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Present	216	15.3	39.0	5.5	131.3	27.7	194.7	67.6
Absent	212.2	18.4	41.6	3.9	136.1	36.4	185.2	64.2
P Value	0.4512		0.0624		0.8691		0.5885	

The relationship between diabetes mellitus and lipid profile patients were found to be statistically not significant the graphical representation is shown in figure.16

Figure.16



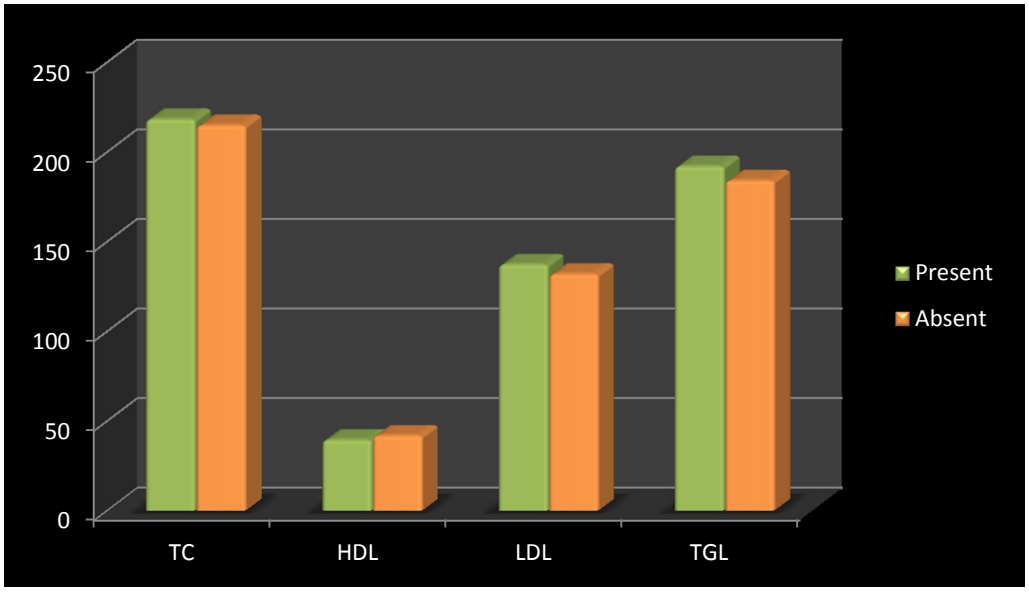
Statistical analysis using student unpaired t-test shows that the p value is greater than 0.05; the drug used in diabetes mellitus and lipid profile patients were found to be statistically not significant

Table.17 Hypertension and Lipid Profile

Hypertensive	Total Cholesterol mg/dl		HDL mg/dl		LDL mg/dl		TGL mg/dl	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Present	218.3	10.7	39.5	5.3	137.3	11.8	192.1	26.6
Absent	214.9	10.1	41.9	3.9	132	26	184.1	23.9
P Value	0.5631		0.6667		0.4999		0.662	

The relationship between Hypertension and lipid profile patients were found to be statistically the graphical representation is shown in figure.17

Figure.17



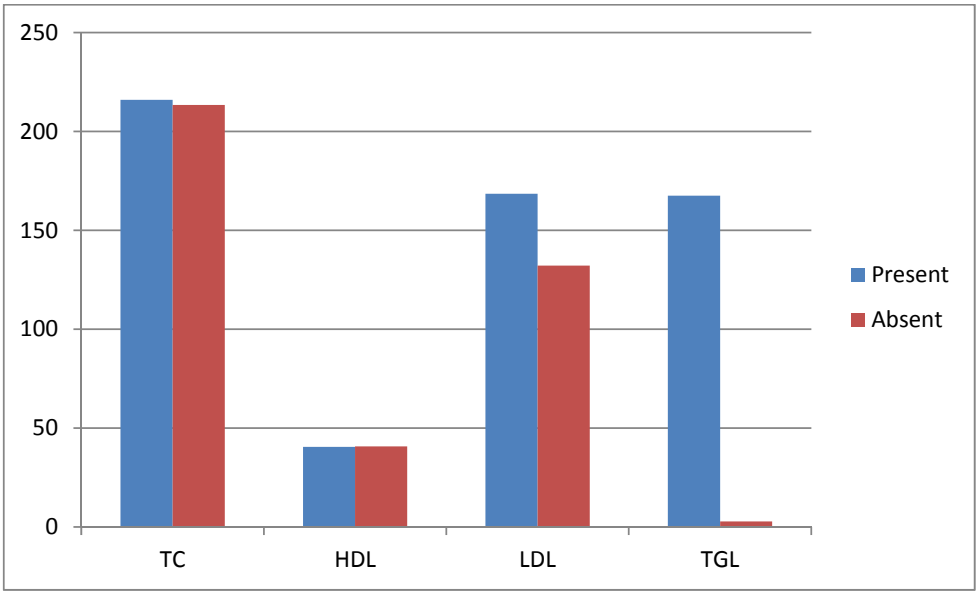
Statistical analysis using student unpaired t-test shows that the p value is greater than 0.05; the drug used in hypertension and lipid profile patients were found to be statistically not significant

Table.18 Family History and Lipid Profile

Family History	Total Cholesterol mg/dl		HDL mg/dl		LDL mg/dl		TGL mg/dl	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Present	216	19.8	40.5	0.7	168.5	59.8	169.5	71.6
Absent	213.4	17.4	40.7	4.8	132.1	30.4	189.8	64.9
P Value	0.803		0.8017		0.1195		0.5633	

The relationship between Hypertension and lipid profile patients were found to be statistically not significant the graphical representation is shown in figure.18

Figure.18



Statistical analysis using student unpaired t-test shows that the p value is greater than 0.05; the drug used in family history and lipid profile patients were found to be statistically not significant

RELATIONSHIP BETWEEN BLOOD PRESSURE AND AFTER VARIABLES

Table.19 Age and BP

Age	SBP mm Hg		DBP mm HG	
	Mean	**SD**	**Mean**	**SD**
<50	133.1	17.6	75.6	8.1
>50	138.5	15.2	76.5	6.5
P value	0.2584		0.5298	

The comparison of Age and BP in Dyslipidemia patients did not show any significant difference. The graphical representation is shown in Figure.19

Figure.19

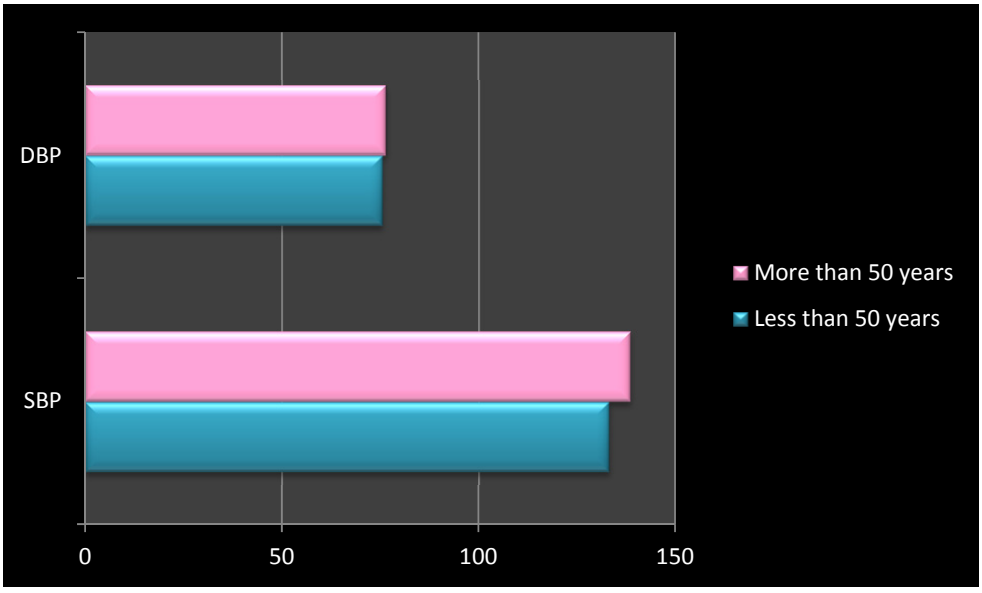


Table.20 Sex and BP

Age	SBP mm Hg		DBP mm HG	
	Mean	**SD**	**Mean**	**SD**
Male	137.4	17.1	76.0	7.4
Female	131.5	12.8	76.9	6.3
P value	0.2048		0.6517	

The comparison of Sex and BP in Dyslipidemia patient did not show any significant difference. The graphical representation is show in Figure.20

Figure.20

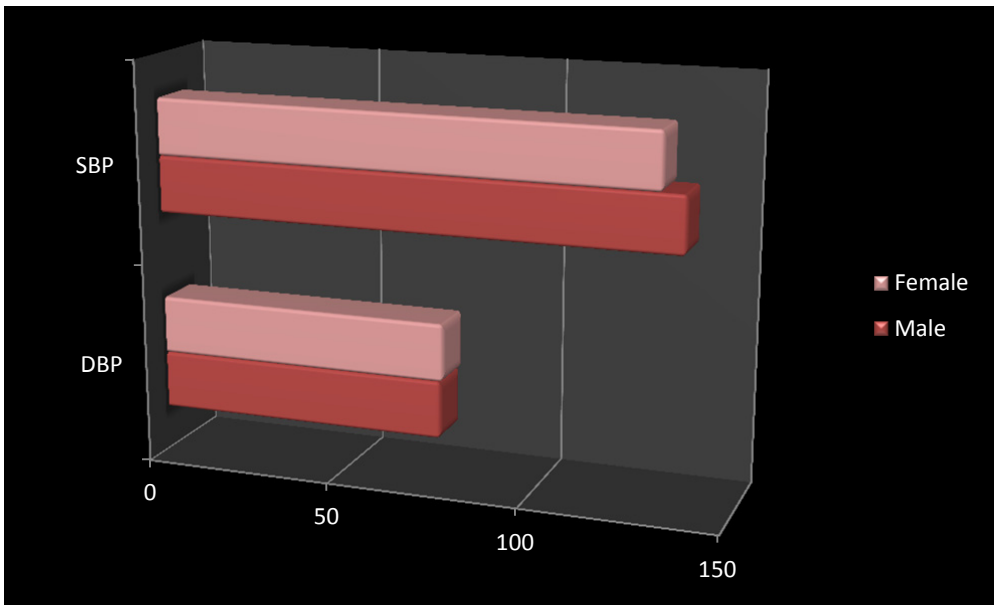


Table.21 Diabetes Mellitus and BP

DM	SBP mm Hg		DBP mm HG	
	Mean	**SD**	**Mean**	**SD**
Present	141.0	15.5	78.5	5.9
Absent	133.8	16.4	75.0	7.5
P value	0.0836		0.0526	

The comparison of DM and BP in Dyslipidemia patients did not show any significant difference. The graphical representation is show in Figure.21

Figure.21

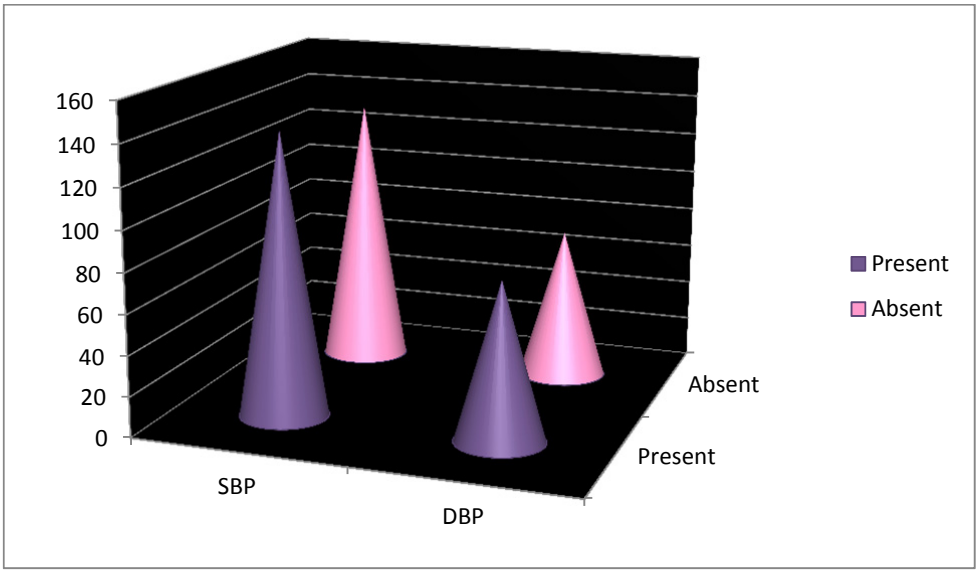


Table.22 Hypertension and BP

Hypertensive	SBP mm Hg		DBP mm HG	
	Mean	**SD**	**Mean**	**SD**
Present	142.2	14.1	75.6	7.5
Absent	129.3	16.3	75.7	6.9
P value	0.002		0.6913	

The comparison of Hypertension and systolic BP in Dyslipidemia patients were found to be statistically significant. But the diastolic BP did not show any significant difference. The graphical representation is show in Figure.22

Figure.22

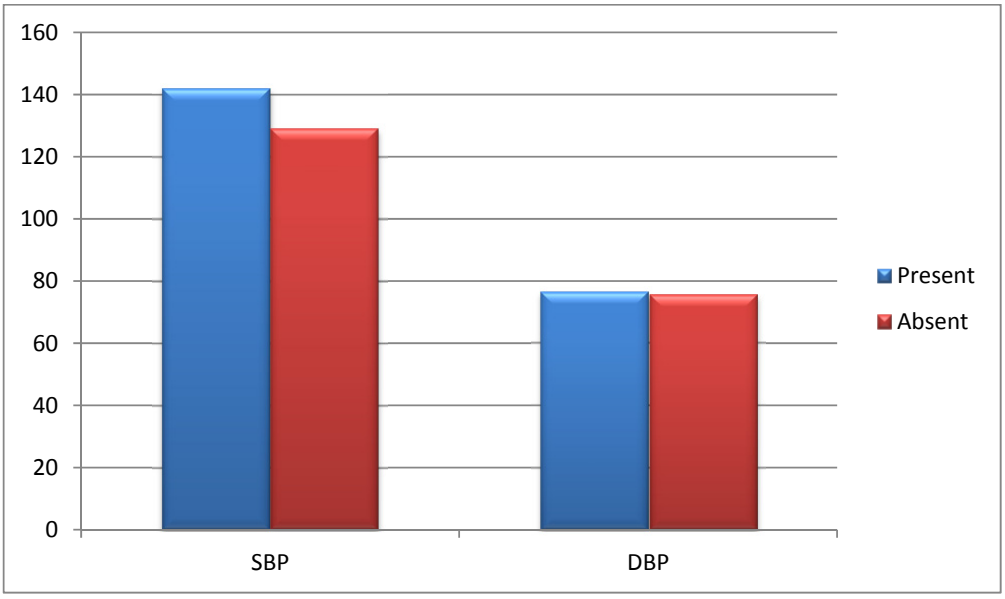
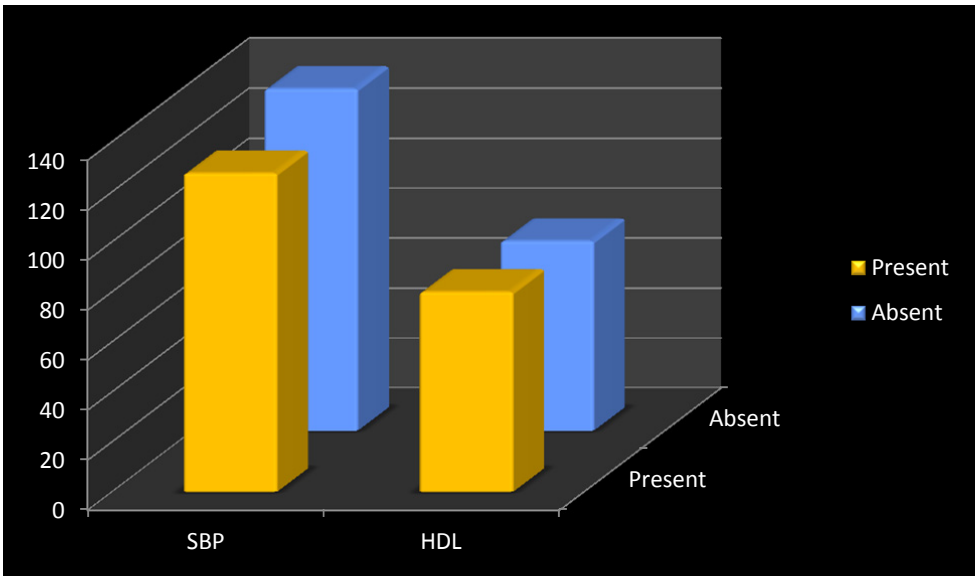


Table.23 Family History and BP

Family History	SBP mm Hg		DBP mm HG	
	Mean	**SD**	**Mean**	**SD**
Present	127.5	20.6	80.0	8.2
Absent	136.8	16.1	75.9	7.1
P value	0.3127		0.2921	

The comparison of Family History and BP in Dyslipidemia patients did not show any significant difference. The graphical representation is show in Figure.23

Figure.23



CHAPTER IX

DISCUSSION

9. DISCUSSION

The present study was designed to primarily compare efficacy, safety and quality of life of Pitavastatin versus Atorvastatin at the doses prescribed in routine clinical practice. Due to the observational nature of this study, dose-to-dose comparisons between Pitavastatin and Atorvastatin relied mainly on the sample size available in each of the comparator groups. The sample size a comparison between Pitavastatin 1 mg and Atorvastatin 20 mg with Pitavastatin 2 mg and Atorvastatin 40 mg.

This was a randomized controlled study, there were some baseline differences between Pitavastatin and Atorvastatin treated patients. Patients were matched on relevant characteristics and co morbidities before their data were abstracted. After accounting for age, sex, pre index lipid levels, the risk, and therapy duration, present reductions in lipid level remained significantly greater with Pitavastatin compared with Atorvastatin.

In the present study, patients treated with Pitavastatin were more likely to attain lipid the lower level than were patients who received Atorvastatin, which was statistically significant after accounting for baseline differences between groups. The Pitavastatin -treated patients continued to achieve significantly greater goal attainment rates before and after accounting for baseline differences.

The results of the present study showed Pitavastatin to produce greater reductions in lipid levels, namely LDL cholesterol, Total Cholesterol, HDL and Triglycerides goal attainment rates compared with Atorvastatin.

The present study found greater reduction in lipid level with Pitavastatin 1 -2 mg compared with Atorvastatin 20 - 40 mg.

The findings of the present study provide valuable information in aiding decisions on therapeutic drug selection for patients with Dyslipidemia in actual clinical practice settings. Furthermore, diet and exercise could also influence the results of patients' lipid levels.

We Classified patients by the risk and assigned them a lipid goal using clinical data obtained from their medical records. Although medical record data are

considered high quality, we could not ascertain if some vital information were missing from the medical records. This may have led to some biases that could not be assessed.

Results of the study showed Pitavastatin 1 -2 mg to be a cost-effective alternative to Atorvastatin 20-40 mg, both in terms of cost per percentage lipid level reduction and cost per patient achieving. These results are in line with several previous cost-effectiveness analyses, which reported Pitavastatin to be more cost effective than Atorvastatin, Pravastatin and Simvastatin. Further economic analyses of Pitavastatin are now needed to determine its potential as more cost-effective therapy compared with other statins.This study reveals that Pitavastatin at doses of 1 - 2 mg was superior to Atorvastatin 20-40mg based therapies, as it reduced LDL-Cholesterol by more than the dose of Atorvastatin. Similarly, it reduced triglycerides and total cholesterol more than Atorvastatin therapy and increased HDL by the lower two doses more than was achieved on Atorvastatin therapy. These results are better at lower but not at higher dose than these seen in the comparative study of statins in a general population, which showed equivalence of 1 mg Pitavastatin and 20 mg Atorvastatin.

Changes in total cholesterol

The present study was found that low dose of Pitavastatin 1 mg changes the total cholesterol level as 22.1%. Whereas Pitavastatin 1 mg is better than Atorvastatin 20 mg in the reduction of total cholesterol.And also found that low dose of Pitavastatin 2 mg changes the total cholesterol level as 25.4%. Whereas Atorvastatin 40mg changes the total cholesterol level 22.7%. It shows that Pitavastatin 2 mg is better than Atorvastatin 40mg in the reduction of total cholesterol which is mentioned in table no: 7

Changes in HDL Level

The present study was found that low dose of Pitavastatin (1 mg) changes the HDL level as 16.8%. Whereas Atorvastatin (20mg) changes the HDL Level 4.9%. It Shows the Pitavastatin (1 mg) is better than Atorvastatin (20mg) increase of HDL.And also found that low dose of Pitavastatin (2 mg) changes the HDL Level as 20.9%. Whereas Atorvastatin (40mg) changes the HDL Level 11%. It shows that

Pitavastatin (2 mg) is better than Atorvastatin (40mg) increase of HDL which is mentioned in table no: 8

Changes in LDL Level

This study was found that low dose of Pitavastatin (1 mg) changes the LDL Level as 22.6%. Whereas Atorvastatin (20mg) changes the LDL Level 16.6%. It shows that Pitavastatin (1 mg) is better than Atorvastatin (20mg) in the reduction of LDL.And also found that low dose of Pitavastatin (2 mg) changes the LDL Level as 33%. Whereas Atorvastatin (40mg) changes the LDL Level 28%. It Shows that Pitavastatin (2 mg) is better than Atorvastatin (40mg) in the reduction of LDL which is mentioned in table no:9

Changes in Triglycerides Level

This study was found that low dose of Pitavastatin (1 mg) changes the Triglycerides Level as 13.8%. Whereas Atorvastatin (20mg) changes the Triglycerides Level 7.9%. It shows that Pitavastatin (1 mg) is better than Atorvastatin (20mg) in the reduction of Triglycerides.And also found that low dose of Pitavastatin (2 mg) changes the Triglycerides Level as 20.8%. Whereas Atorvastatin (40mg) changes the Triglycerides Level 10.1%. It shows that Pitavastatin (2 mg) is better than Atorvastatin (40mg) in the reduction of Triglycerides which is mentioned in table no: 10

Dyslipidemia in Diabetes Mellitus

Diabetes mellitus is well recognized risk factor for Dyslipidemia. In the present study the diabetes alone was not an independent risk factor for the development of Dyslipidemia. There was no significant difference between diabetics and non-diabetics.

Dyslipidemia in Hypertension

The comparison of Dyslipidemia in Hypertensive and Non Hypertensive patients did not show any significant difference.

Incidence of side effects

Both Pitavastatin and Atorvastatin were well tolerated in this study, and none of the reported side effects were unexpected, given the age and underlying medical conditions of the patient population. Most side effects were of mild or moderate severity, and were not considered to be treatment-related. The most commonly reported side effect was myalgia, headache.

CHAPTER X

CONCLUSION

10 Conclusions

Patients treated with Pitavastatin had significantly greater reductions in LDL cholesterol, total cholesterol, triglycerides levels compared with those receiving Atorvastatin. Patients receiving Pitavastatin were more likely to attain lipid goals compared with patients treated with Atorvastatin

The recommended starting doses, Pitavastatin (1-2 mg) is more efficacious than Atorvastatin (20-40 mg), in terms of cholesterol, HDL, LDL, and TG better in the lipid profile. The greater efficacy of Pitavastatin at starting dose should help to reduce the need for higher dosage and enable more Patients to achieve recommended treatment goals in clinical practice. Moreover there is, improvements in the whole lipid profile, including rise in HDL-C.

CHAPTER XI

SUGGESTIONS

11. SUGGESTIONS

Suggestions for the management of Dyslipidemia,

1. Regular exercise
2. Lifestyle modification
3. Proper intake of drug to control disease
4. Initially physician may start with the dose of Pitavastatin 2 mg for the patients of Dyslipidemia and then they can reduce the dose of Pitavastatin to 1 mg to maintain the cholesterol level.

CHAPTER XII

BIBLIOGRAPHY

BIBLIOGRAPHY

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APPENDIX

PATIENT HISTORY PROFORMA

NAME OF PATIENT :

DATE OF BIRTH :

AGE IN YEARS :

SEX (F/M) :

MARITAL STATUS : MARRIED/UNMARRIED

OCCUPATION :

CONTACT ADDRESS :

CONTACT NUMBER :

DATE OF ADMISSION:

TODAY'S DATE :

HOSPITAL NUMBER :

DIAGNOSIS :

CURRENT MEDICATIONS :

OTHER MEDICAL ILLNESS, CURRENT OF PAST:

FAMILY HISTORY :

SMOKERS (CURRENT/EX) :

NUMBER OF YEARS OF SMOKING:

DURATION OF DYSLIPIDEMIA (YEARS):

PREVIOUS HISTORY OF CHD (YES/NO):

STUDY DRUG

LABORATORY INVESTIGATION

LIPID PROFILE	**1st visit**	**2nd visit**	**3d visit**
TOTAL CHOLESTEROL LEVEL			
HDL CHOLESTEROL LEVEL			
LDL CHOLESTEROL LEVEL			
TRIGLYCERIDES LEVEL			
BLOOD PRESSURE			

ADVERSE EVENTS

VISIT 2 (WEEK 9) □ YES □NO **VISIT 3 (WEEK 20) □ YES □NO**

IF YES PLEASE SPECIFY:

Page number	Line number	Printed as	Read as